

NEOPLASMS OF BONE

AND RELATED CONDITIONS

Their etiology, pathogenesis, diagnosis, and treatment

By BRADLEY L. COLEY, M.D.

*Attending Surgeon, Bone Tumor Department, Memorial
Hospital for Cancer and Allied Diseases. Assistant
Professor of Clinical Surgery, Cornell.*

WITH 622 ILLUSTRATIONS AND 53 TABLES



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NEOPLASMS OF BONE

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To the memory of my father
DR. WILLIAM BRADLEY COLEY
this book is gratefully dedicated

PREFACE

IT HAS SEEMED TO THE AUTHOR THAT THERE IS A NEED FOR ASSEMBLING AND compiling our present-day knowledge of the complex field represented not only by the true neoplasms of bone, both benign and malignant, but also by the diverse group of conditions affecting the skeletal system with which true tumors of bone are so often confused.

The average practitioner encounters too few cases to enable him to gain a wide personal experience in their diagnosis and treatment; indeed, the same may be said of many of the large general hospitals and clinics.

The author has been singularly fortunate in having had the opportunity to see and treat an unusual concentration of these cases during a period of the last twenty-five years spent in the Bone Tumor Department of Memorial Hospital. It is the knowledge or impressions gained from this rich experience that he feels impelled to share with those of the profession who are called upon to diagnose and treat sufferers with tumors of bone.

The purpose of this book, therefore, is to present the subject of bone neoplasms in a form that will be of value not only to the oncologist but also to the orthopedist, the radiologist, the general surgeon, and the general practitioner.

While bone sarcoma is fortunately an uncommon condition it is a most serious one with a high mortality rate. It seems reasonable to assume that this present high rate can be materially lowered by an earlier recognition and more prompt treatment of the condition. It is no exaggeration to say that nearly half of the cases of osteogenic sarcoma have the disease in *detectable form* for more than six months before a correct diagnosis is made. One can only speculate on the favorable effect on survival rates were this period of time cut in half. This, the author believes, could be accomplished by a keener realization of the significance of the early symptoms and a wider tendency to insist upon early roentgenographic examination when these symptoms are present.

Little emphasis has been placed on microscopic pathology because there are several standard works which cover this phase in considerable detail; to mention two: *Neoplastic Diseases* by Ewing, and *Tumors of Bone* by Geschickter and Copeland. The author has thought it best to devote more attention to the clinical aspects, to cite the difficulties of early diagnosis, the

PREFACE

asures required to reach a diagnosis, the various therapeutic indications and techniques, and finally, the results of treatment. Yet the essential nature of the assistance rendered by the pathologist is too obvious to require comment. The constant aid rendered us by Fred W. Stewart and Frank W. Foote in the review of equivocal cases and in the histologic interpretation of material as a whole has been of the utmost value and is acknowledged with great appreciation.

The inclusion of a variety of nonneoplastic conditions involving the skeletal system is intended to afford the reader a knowledge of those lesions with which tumors of bone are at times confused. While many of them are uncommon and some are decidedly rare, they are regarded as necessary to a comprehensive study of the whole field.

The importance of illustrations and their superiority over written descriptions is nowhere more evident than in the field of bone tumors where the roentgenogram is such a vital factor in differential diagnosis. The Chinese are credited with an old saying that "one picture is better than a thousand words." Therefore a comparatively large number of roentgenograms have been reproduced to show the wide variations in the appearance of a single type of tumor, e.g., osteogenic sarcoma, depending on factors inherent in the tumor itself which affect the propensity for destroying bone, for producing sequestra or for causing reactive bone formation on the part of osseous tissue adjacent to the tumor itself. Moreover, for the sake of completeness, it seems to the author appropriate to depict not only the common varieties but the unusual, and even the rare ones. Prior to the advent of the roentgenogram surgeons had little conception of these differences until the limb had been amputated and the pathologist had completed his study of the gross and microscopic specimens.

Recent advances in the interpretation of changes in the chemical constituents of the blood have been conspicuously helpful in the preoperative study of a number of types of bone tumor, and it seemed fitting to devote a chapter to a detailed consideration of the role played by blood chemistry. To the author of this chapter, Helen Q. Woodard, deepest gratitude is expressed not only for this undertaking but for her many years of helpful cooperation in the Bone Tumor Department of Memorial Hospital. The author assumes full responsibility for the ideas and concepts expressed in this volume. At the same time he is aware that others with wide experience in the subject may hold different views on many points. It should be emphasized that there are many important gaps in our knowledge, many controversial matters, and one may confidently predict that the views held today may be altered materially in the future.

In few fields of medicine has the accumulated knowledge been the contribution of such a multitude of observers. Space will not permit naming them here but we should not be unmindful of our indebtedness to them. To

those leaders who have been an inspiration and a help to the author and whom he has had the rare privilege of knowing personally he wishes to acknowledge his gratitude; they include Ewing, Codman, Bloodgood, William B. Coley, Phemister, Meyerding, Stewart, Jaffe, Stout, Foote, Platt of England, and Ivanissevich of Buenos Aires.

To Norman L. Higinbotham who has long been associated with the author at Memorial Hospital and who has compiled and recorded valuable data it is a pleasure to express deepest appreciation.

Grateful acknowledgment is also paid to Major General Norman T. Kirk for granting permission to use material from hospitals of the United States Army, to Clarence Halter of the Photographic Department, Memorial Hospital, for his help with the illustrations, and to Sigmund Epstein for supplying reproductions of prehistoric and other early examples of tumors of bone in animals and in man.

We appreciate Hayes E. Martin's permission to use statistics and material on jaw tumors from the Head and Neck service of Memorial Hospital of which he is attending surgeon in charge.

Much of the difficult task of compiling the bibliography and of the actual preparation of the manuscript was cheerfully assumed by my secretary, Miss Florence Best, without whose encouragement and constant efforts this book would most certainly never have been completed. My gratitude to her cannot be fully expressed.

It is a pleasure to express appreciation to the publisher, Paul B. Hoeber, and to his editor, Brian M. Heald, for their patience and cooperation in every phase of this undertaking.

Finally the author wishes to pay homage to his father, the late William B. Coley, who devoted more than forty years of his life to the relief of those afflicted with bone sarcoma. Much was learned from a close association with him over a period of seventeen years. While his efforts to develop a cure for the disease were not successful, he was a pioneer in investigations of the treatment of malignant tumors by bacterial products. The future may well show that his ideas were sound. But he will be remembered primarily for the part which he played in establishing the first cancer research project in America, the Collis P. Huntington Fund for Cancer Research. To him and to the others who have contributed so much to our knowledge of tumors of bone the author is profoundly grateful.

BRADLEY L. COLEY

New York City

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INTRODUCTION TO SECTION ONE

ONE OF THE MOST IMPORTANT MILESTONES ALONG THE PATH OF PROGRESS in the acquisition of more accurate knowledge of bone neoplasms was the establishment, in 1922, of the Bone Sarcoma Registry of the American College of Surgeons. The moving spirit behind this project was Ernest Amory Codman of Boston who conceived the idea and succeeded in implementing it. With unflagging energy he devoted himself, as the first Registrar, to the task of making the Registry a means by which the accumulated knowledge of a group of rare diseases could be pooled, studied, and evaluated for the benefit of all. These diseases are so unusual that comparatively few members of the profession have an opportunity to see enough cases to become proficient in diagnosis or to know what to expect from the various methods of treatment.

In the period preceding the founding of the Registry there was considerable uncertainty as to the degree of malignancy of such conditions as giant cell tumor. There was little understanding of the different varieties of primary bone sarcoma, and the identity of the specific lesion now known as Ewing's sarcoma (endothelioma of bone) had not yet been established. The Registry was able to classify the cases which were submitted in considerable numbers from all parts of the United States and Canada. The diagnosis was established after a study of each individual case by a board of surgeons and pathologists experienced in the field of bone neoplasms. Generally the final decision in doubtful cases rested upon the microscopic interpretation, although the history, physical findings, and roentgenograms were submitted along with microscopic sections.

Among those who served on the original committee and who were responsible for many of the early diagnoses were Bloodgood, Ewing, Mallory, and Codman. Early in its history the Registry issued a *Classification of Malignant Bone Tumors*; in 1939 this was revised and enlarged to include benign neoplasms of bone.

Among the important results of the Registry the following seem particularly noteworthy:

Its nomenclature made it easier for members of the profession to know what types were being referred to in discussions or publications.

It pointed out that the so-called "giant cell sarcoma" of earlier days was not a sarcoma but a benign tumor, thus helping to establish the present designation "benign giant cell tumor." As a result of this conception there were fewer amputations performed as a primary measure and fewer limbs were sacrificed.

It did much to standardize treatment. The average surgeon with but limited experience in this field was able to ascertain which methods produced the best results in a carefully followed series drawn from clinicians scattered all over the country and from a few centers where an unusual concentration of these cases occurred.

It also afforded any interested surgeon, radiologist, or pathologist a reservoir of carefully selected material which had been classified and traced over a long period of time and which he could study from a number of different standpoints.

Finally, it provided a consultation service to the relatively inexperienced doctor who sought advice from the Registry in the treatment of his cases, although advice obtained by this method sometimes constituted a hazard and was frequently referred to as "mail-order diagnosis."

The activities of the Registry in recent years have slackened somewhat, due to the fact that only those cases that are considered exceptional, or at least out of the ordinary, are deemed acceptable for registration. This restriction of activity is understandable for in the last quarter of a century, or since the Registry's inception, a sufficiently large number of cases have been classified and registered to furnish a huge storehouse of material and make it unnecessary to continue this process indefinitely.

It is difficult to estimate the role which the Registry has played in the progressive widening of our interest and knowledge of bone neoplasms but it seems to the author that it transcends the contribution of any one individual and has influenced and aided many who have themselves made distinct advances in the field of oncology.

ORIGIN AND STRUCTURE OF BONE

Bone is a highly specialized mesoblastic tissue whose density and hardness represent an adaptation of structure that permits connective tissue to be sufficiently strong to bear bodyweight, to act as fixed points for the action of muscles, and to protect vital portions of the body.

When the mineral content of the bone is dissolved by an agent such as Perenyi's fluid, there is left the connective tissue which is the basis from which most primary tumors of bone originate.

In considering the life history of bone, it is well to recall that it commences as a condensed mesoblastic tissue which contains a variable amount of cartilage. The proportion of cartilage increases as growth proceeds until a virtual cartilaginous cast of the later bone is formed. Blood vessels pene-

trate this relatively avascular tissue, enter the center of the shaft through an opening which later becomes the nutrient foramen, and reach the ends of the bones through smaller apertures (epiphyseal canals).

This vascularization stage marks a transition of great significance for with the entrance of the blood vessels and the contact of blood with the cartilage cells a change comes over the cytoplasm—it disintegrates and the cartilage cell now acquires the property of assimilating calcium and of depositing it in the surrounding tissue. The osteoblast is now active. The process extends centrifugally from the middle of the shaft and independently at each epiphysis.

The anatomical divisions of a growing bone that must be borne in mind are the epiphysis, the diaphysis or shaft, and the metaphysis which is that portion of the shaft adjacent to the epiphyseal plate of cartilage.

The periosteum, or enveloping fibrous membrane, is an important structure. Directly beneath it and outside of the underlying bone there is a potential space which contains osteoblasts. Though these are constantly present, they vary in numbers and in activity. For instance, when there is an acute infection in the medulla they pour into the subperiosteal space in large numbers, while in the early phases of periosteal infection, or after acute trauma, they leave this area for the interior of the bone. It is considered probable that there is a constant flow to and fro of osteoblasts into and from the subperiosteal space by means of the tiny canaliculi and the more specialized haversian and Volkmann's canals.

Where the epiphysis joins the shaft, there is a disclike plate, the epiphyseal cartilage; the area where this cartilage makes contact with the shaft or diaphysis is the metaphysis. It is this latter area which is of special interest and importance since it is here that activity is manifest throughout the period of bone growth, and it is the site at which bone pathology originates, including scurvy, rickets, acute pyogenic infections, tuberculosis, and certain benign and malignant tumors. In structure it is a vascular space lined by a single layer of endothelium. Here there are projections and recesses which permit circulating body fluids to come into direct contact with the cartilage cells of the epiphyseal plate and it is here that these same cells take on the characters and functions of osteoblasts. It is here that, as long as the bone continues to elongate, the same process continues as was seen in the first phases of ossification of fetal bone.

Cortical or compact bone may be described as a dense conglomeration of sheets of connective tissue in lamellar arrangement impregnated with lime salts. They are grouped concentrically around canals or fill the spaces between the whorls. Between the lamellae are the lacunae containing the relatively large bone cells which have processes that extend into the canaliculi. Though these bone cells probably play an important role in the nutritive processes of bone, they are not known to have bone-forming prop-

erties. They are thought to be homologous with the cells of ordinary connective tissue. They may be identical in their derivation with the osteoblasts but, locked in the lacunar spaces, have become altered in function and in appearance. Nevertheless, true osteoblasts are to be found scattered throughout the bone, in spaces and canals, in the medulla, beneath the periosteum, in perivascular spaces, and even in lacunae.

The marrow is a complex structure intimately concerned with production of blood cells. This area may give rise to tumors which originate in its reticulum, in the endothelial cells of its vascular and lymphatic spaces, and in some of the specialized cells that are formed there. Among these tumors may be mentioned Ewing's sarcoma (endothelioma), reticulum cell sarcoma, liposarcoma, plasma cell myeloma, erythroblastoma, lymphocytoma, and myelocytoma.

This composite tissue, bone, is subject to a coincident tissue growth and absorption which is finely coordinated and which comprises a balanced process of anabolism and catabolism, a constant subperiosteal and endosteal growth. It is not surprising, therefore, that this delicate balance can be upset by such influences as trauma, or possibly by biochemical or other environmental changes as yet unknown, with a resulting growth alteration which we recognize as tumor formation.

For a more detailed account of bone metabolism, particularly as it relates to blood chemistry, see pages 51-53.

Normal bone is composed of an organic matrix in which is deposited a calcium-phosphate-carbonate salt. It has three types of surface, one on which nothing is happening, one on which bone is being resorbed, and one on which bone is being formed. Where bone is being resorbed osteoclasts are seen. Bone formation consists of two steps—laying down of matrix by osteoblasts and deposition therein of calcium salt. Resorption and formation occur simultaneously. The reason why calcium can be resorbed on one surface and deposited on another is probably connected with the activity of the enzyme phosphatase.

There is evidence that stresses and strains strongly stimulate the osteoblasts to lay down bone matrix; the greater the stresses and strains the greater the bone formation. Hence persons whose occupation involves considerable physical activity have heavy skeletons and those with sedentary occupations tend to have light bones.

Osteomalacia is a failure of deposition of calcium salts in this matrix. Osteoporosis is an underactivity of the osteoblasts in laying down bone matrix. Among the causes of osteoporosis may be listed the following:

Old age

Inactivity (immobilization)

Lack of estrin stimulation (postmenopausal osteoporosis)

Lack of protein to provide material for the matrix (Cushing's syn-

drome, osteopathies of starvation, demineralization of hyperparathyroidism)

Usually there is no alteration of calcium and phosphorus levels in osteoporosis but since resorption continues and bone formation decreases, hypercalcaemia results.

Resorption of bone and reconstruction of osseous tissue are seen most prominently in the spongiosa of the bones of growing animals, although it is by no means confined to this portion of the bone. Many observers have noted an association of osteoclasts and have felt that these had a causal relationship to resorption itself. However, McLean and Bloom, in their experiments on resorption and reconstruction of bone under physiologic conditions in young animals, saw no evidence of decalcification preliminary to resorption of the organic matrix. Bone salt and matrix both disappeared together and the persisting portions of the trabeculae were fully calcified. They observed no evidence of phagocytosis of bone salt by osteoclasts.

The term myelofibrosis means fibrosis of bone marrow. It may be primary or secondary, localized or diffuse, mild, moderate or severe. It may be associated with some degree of proliferation of endosteal bone (osteosclerosis).

It may occur in a wide variety of conditions, as tabulated by Erf and Herbut, who list more than sixty separate instances of circumstances with which it may be associated; many of these are of concern to those who encounter tumors of bone or other skeletal derangements at times confused with neoplasms. The following is modified from their list:

LOCALIZED	GENERALIZED
<i>Primary (idiopathic):</i> Fibrous dysplasia (Albright's syndrome) Monomelic medullary osteosclerosis	<i>Primary</i> Group of diseases of hemopoietic system associated with anemias, leukemias, and splenomegalias.
<i>Secondary to:</i> <ul style="list-style-type: none"> Bone Diseases <ul style="list-style-type: none"> A. Localized fibrocystic disease B. Localized osteitis deformans C. Bone infections <ul style="list-style-type: none"> (1) Chronic osteomyelitis (2) Sclerosing osteitis (3) Syphilis (4) Yaws (5) Osteoid osteoma D. Tumors <ul style="list-style-type: none"> (1) Sclerosing osteogenic sarcoma (2) Enchondroma (3) About pathologic fracture E. Aseptic necrosis <ul style="list-style-type: none"> (1) Occlusion of nutrient vessel (2) Postradiation necrosis of bone 	<i>Secondary to:</i> <ul style="list-style-type: none"> Generalized parotic conditions <ul style="list-style-type: none"> A. Osteogenesis imperfecta B. Infantile scurvy C. Renal rickets D. Osteomalacia E. Hyperparathyroidism Generalized sclerotic conditions <ul style="list-style-type: none"> A. Osteopetrosis B. Melorheostosis C. Osteitis deformans D. Leontiasis osseum Metastatic lesions of bone <ul style="list-style-type: none"> A. Lytic B. Sclerotic

It is apparent that the exact cause of an individual case of myelofibrosis may be impossible to determine from a microscopic section and it is necessary to reach conclusions on clinical, radiographic, and laboratory findings of morphology and chemistry of blood.

It is well to appreciate that fibrosis of marrow can be produced by so wide a diverse group of conditions.

DEFINITION OF BONE TUMOR

A tumor of bone may be defined as a new growth arising in a bone or derived from cells which are in or on the bone. e. Common usage
those derived from

cells in the marrow and from the specialized connective tissue which covers the bone, the periosteum.

According to this definition, neoplasms of bone include those which arise from the primitive bone cell or osteoblast, the primitive cartilage cell or chondroblast, and the primitive connective tissue cell or fibroblast. Also included are tumors which have their origin in the blood vessels of bone (the angiomas and endotheliomas) and those which spring from cells composing red marrow (the myelomas) and yellow marrow (the liposarcomas). Likewise included are tumors which occur in bone by virtue of having spread there from some other organ by direct invasion or by metastasis.

A primary bone tumor is one which originates in bone while a metastatic tumor is one which begins elsewhere and reaches bone through transfer of its cells by way of the blood stream or by lymphatics.

Benign tumors of bone do not invariably retain their innocent characteristics. Some may take on malignant qualities several years after their inception, and thereafter behave as do any other malignant tumors. Other instances may be cited where, by virtue of its size or location, a benign tumor may lead to a fatal outcome. An example of the latter is the case of a benign cartilaginous tumor, or osteochondroma, of the sella turcica which eroded a major cerebral artery in the circle of Willis and caused a fatal intracranial hemorrhage.

There are a number of conditions of bone in which it is difficult to decide whether or not they should properly be classed with the true neoplasms. Such entities as fibrous dysplasia, bone cyst, melorheostosis, osteoid osteoma, eosinophilic granuloma, the lipid storage diseases of bone (Gaucher's disease, Niemann-Pick's disease), leontiasis ossea, and others may not deserve inclusion among the neoplasms of the skeletal system. However they, as well as a considerable number of lesions which are unquestionably not neoplastic, have been included in this treatise simply because they are thought worthy of consideration as they may give rise at times to difficulties in diagnosis and may be confused with true tumors of bone. Moreover, secondary bone sarcomatous alteration may occur as a complication in a

number of these (see p. 213 and Figs. 33, 73, and 76). Probably the most frequently encountered example of malignant alteration in a nonneoplastic disease of bone is Paget's disease (osteitis deformans).



FIG. 1. Earliest known tumor of bone occurring between two caudal vertebrae of a large dinosaur. All traces of the intervertebral junction are obliterated and the tumor has firmly united the two bones in a solid mass. This specimen was collected from the Como beds, Comanchean, of Wyoming by Dr. S. W. Williston at the time when these deposits were at the height of their fame as dinosaur quarries. Reproduced from *Antiquity of Disease* by Roy L. Moodie.

HISTORICAL

The earliest known neoplasm of bone is that described by Moodie as occurring between two caudal vertebrae of a large dinosaur from the Comanchean period of the Mesozoic era. This was a hemangioma which in man has a predilection for the vertebral column (see Fig. 1).

The next oldest example, an osteoma involving the dorsal vertebra of a Cretaceous dinosaur, is the only one thus far found in a fossil condition. Smith and Dawson refer to an osteogenic sarcoma in an Egyptian mummy from the 5th dynasty (circa 2500 B.C.) (see Fig. 2). This is probably the oldest known bone sarcoma in man.

We know of no other references to the existence of malignant tumors of bone in man prior to the middle of the third century after Christ. Ruffer describes in some detail a pelvic osteosarcoma in an Egyptian mummy unearthed in the catacombs of Kom el Shougafa in Alexandria, which he believes dates from Roman times (A.D. 250). This tumor involved the right pelvic bone, particularly the ischium and lower portion of the ilium, was partly solid, partly cystic, deeply situated, and encroached upon the obturator and acetabulum (see Fig. 3). Reasoner refers to this case and assumes it to be the earliest record of a malignant neoplasm in man.



FIG. 2. The first known malignant bone tumor in man; an osteogenic sarcoma of the femur in an Egyptian mummy of the 5th dynasty (circa 2500 B.C.). (See Fig. 64 in *Egyptian Mummies* by Smith, G.E. and Dawson, W.R., London, Geo. Allen and Unwin, 1924.)



FIG. 3. Oldest known bone tumor of pelvis in man; pelvic osteosarcoma in an Egyptian mummy, unearthed in the catacombs near Alexandria. Presumed to date from Roman times (A.D. 250). (From Ruffer's *Studies in the Palaeopathology of Egypt*, University of Chicago Press, 1921.)

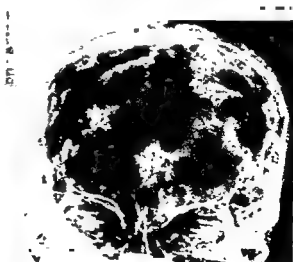


FIG. 4. Multiple myeloma in a 60-year-old Iroquois Indian (circa A.D. 900). Photograph and anteroposterior roentgenogram of skull. Note multiplicity of defects in skull. (Ritchie and Warren—see Bibliography.)

An example of a multiple myeloma occurring in a pre-Columbian Iroquois Indian (Fig. 4) and an osteogenic sarcoma of the cranium of a Peruvian Indian of the same period (Fig. 5) are included.



FIG. 5. Osteosarcoma of frontal and parietal bones in a pre-Columbian Indian, Peruvian. (MacCurdy quoted by Moodie—see Bibliography.)

Two interesting bone tumors of the eighteenth and nineteenth centuries are also depicted (Figs. 6-7).

While the terminology used to describe these tumors differs from present-day nomenclature it is not difficult in most instances to determine the type represented.

Sarcoma is a malignant tumor comprised of connective tissue cells. *Osteosarcoma* was a term first employed by Boyer who applied it to certain malignant bone tumors. Astley Cooper, somewhat earlier, recognized that there were medullary and periosteal tumors of bone, although clinicians prior to his time had made only partially successful attempts to distinguish between primary sarcomas, secondary carcinomas, and inflammatory conditions of bone. It was Lebert, in 1845, who pointed out microscopic differentiations between sarcoma and carcinoma of bone. Virchow described the morphology of bone sarcoma in detail.

Nélaton (1860) was the first to recognize giant cell tumors as being a specific group with benign characteristics. His views, contrary to those of Billroth, were sustained by Gross (1879). According to Ewing, "Gross' description of the origin, structure, clinical characters and treatment of bone sarcoma stands today as the classic contribution to this subject."

Among the earlier contributors to our knowledge of bone tumors should be mentioned: Paget, Recklinghausen, Ribbert, and Robin.



6. Rapidly growing chondroma of humerus. (A. Nélaton—see Bibliography.)



Multiple chondromas of hand and fingers. (Marcus Aurelius Severinus' *De Recondita Abscessum Natura*—see Bibliography.)

With the advent of roentgenography coupled with advances in microscopic interpretation, enormous strides were made in the diagnosis, classification, knowledge of prognosis, and treatment of all forms of bone neoplasms.

In England the names of Brailsford, Lawson Knaggs, Platt, and Elmslie are outstanding, as are those of Nové-Jossierand, Tavernier, and Clunet in France. Germany has contributed Kölliker, Schinz, and Uehlinger. In America it is difficult to name all of the many investigators who have made important contributions to this field; among them are Ewing, Codman, Phemister, William B. Coley, Jaffe, Copeland, Geschickter, Pfahler, Meyerdig, and Bloodgood.

In recent times emphasis has been placed upon biochemical methods, bacteriologic products, and radioactive elements in the experimental fields of cancer research. These agents, however, have as yet failed to provide an effective weapon against malignant diseases of bone. One can only hope for and work towards the discovery of a successful method of combatting the scourge which necessitates so many mutilating operations, which causes so much physical pain and mental anguish, and which is responsible for the death of so many young individuals.

I. CLASSIFICATION

MUCH EFFORT HAS BEEN EXPENDED IN TRYING TO PRODUCE A SATISFACTORY classification of tumors of bone. One of the most widely adopted has been that offered by the committee of the Bone Sarcoma Registry of the American College of Surgeons in 1922. However, the committee has recently reviewed it and introduced changes suggested by later experience. Among these changes are the inclusion of liposarcoma of bone and reticulum cell sarcoma of bone (these were recognized as distinct entities only in recent years); the special recognition of the cartilaginous, calcifying giant cell tumor of Codman (epiphyseal chondromatous giant cell tumor), which is included in a separate group of tumors derived from and producing cartilage; the new group of tumors of blood vessels including angioma of bone (both cavernous and plexiform), angioendothelioma, and Ewing's sarcoma (diffuse endothelioma).

The accompanying tabulation (Table I) represents an inclusion of benign as well as malignant bone tumors. This is done in an effort to sim-

TABLE I
CLASSIFICATION OF BONE TUMORS (AUTHOR'S)*

MALIGNANT	BENIGN
Fibrosarcoma of bone	Nonosteogenic fibroma of bone
Osteogenic sarcoma	Osteoma Osteoid osteoma Exostosis
Primary chondrosarcoma	Chondroma
Secondary chondromyxosarcoma	" "
Malignant giant cell tumor	" "
Endothelioma (Ewing's sarcoma)	Cavernous angioma
Angiosarcoma	Plexiform angioma
Myeloma { plasma cell myeloma myelocytoma erythroblastoma lymphocytoma	
Reticulum cell sarcoma	
Liposarcoma	

* Slight modification of revised classification of the Bone Sarcoma Registry, American College of Surgeons, 1939

ply the classification and to emphasize the varieties of benign tumors that may undergo malignant transformation.

DISTRIBUTION

Nearly every bone in the skeleton has been found to be affected by bone tumors. Osteogenic sarcoma, endothelioma, and giant cell tumor have a predilection for long or pipe bones, especially the femur, tibia, humerus, radius, fibula, and ulna. Less frequently affected are the ilium, scapula, ribs, clavicle, and os calcis, and rarely the skull and vertebral column. Enchondromas excepted, the phalanges of the hands and feet are seldom involved; no typical case of osteogenic sarcoma of a phalanx has come to our notice. Metastatic tumors involve the thoracic cage, vertebral column, skull, and pelvic bones, also the femur and humerus; the bones of the forearm and leg are less often involved, while metastases to the small bones of the hands and feet are rare.

For a further consideration of Tumors in Special Localities see pages 419-480.

PORTION OF BONE AFFECTED

There is a well-recognized tendency on the part of certain types of primary tumors to involve different segments of the long bones (see Table II). This tendency is less marked in the case of metastatic tumors and it is not so well recognized where flat bones are concerned. Nevertheless we are

TABLE II
INTERPRETATION OF BONE LESIONS
ACCORDING TO PORTION OF BONE INVOLVED

<i>Central lesions</i>	
A. Ends of long bones	Bone cyst (unicameral) Central chondroma Giant cell tumor Benign chondroblastoma Metastatic carcinoma
B. Shaft of long bones	Eosinophilic granuloma Metastatic carcinoma Fibrous dysplasia Osteogenic sarcoma
<i>Cortical and subcortical lesions</i>	" "
<i>Periosteal lesions</i>	Periosteal fibrosarcoma Ossifying hematoma Syphilis and yaws Melorheostosis Osteolytic osteogenic sarcoma (advanced)
<i>Diffuse lesions</i>	" "
	Multiple cell myeloma Albers-Schönberg disease Fluoride poisoning

aware of the predilection of osteogenic sarcoma for the metaphyseal region, of giant cell tumor for the epiphyseal, and of endothelial myeloma (Ewing's sarcoma) for the diaphyseal, which knowledge is of value in a differential



FIG. 8. Central chondroma of tibia. Appearance closely resembles giant cell tumor.

diagnosis. Exceptions, however, are not infrequently encountered. Among these may be mentioned the osteolytic form of osteogenic sarcoma occurring in the juxta-articular portion of a long bone which may bear strong resemblance to a giant cell tumor. Certain osteogenic sarcomas in children may involve the shaft for a considerable distance and may present roentgenographic changes entirely compatible with a diagnosis of Ewing's sarcoma. Central chondroma may be located in the region which is involved in giant cell tumor and since both are osteolytic this distinction may be difficult (see Fig. 8).

Metastatic tumors of bone vary somewhat in their distribution depending on the type of tumor and whether it spreads by the blood stream or by lymphatic invasion, or, as in some cases, by both routes.

In general, metastases from breast carcinoma involve the spine, pelvis, and ribs; the upper femora and humeri are less often affected. Prostatic carcinoma affects the spine, pelvis, and skull, with innumerable small foci the rule. The more distal the bone the less apt it is to be affected.

Instances of polyostotic osteogenic sarcoma are rare. In some the time-interval between the appearance of the first and the subsequent tumors leads one to assume that they are independent lesions of multicentric origin. In others it has seemed more likely that embolic metastasis through the lungs to the peripheral circulation has occurred.

Of course, where multiple presarcomatous areas exist, it is not difficult to understand how separate and unrelated malignant transformations can take place, e.g., the development of chondromyxosarcoma from multiple foci of enchondroma.

FREQUENCY

Primary tumors of bone of all types are comparatively infrequent (see Table III). Osteogenic sarcoma is the most common of the primary malig-

TABLE III

MORTALITY STATISTICS OF THE CITY OF NEW YORK—1915

	DEATHS FROM ALL CAUSES		DEATHS FROM CANCER ALL FORMS		CANCER OF BONES AND JOINTS		CANCER ACCESSORY SINUSES		CANCER JAW BONES	
	M	F	M	F	M	F	M	F	M	F
Manhattan	14,093	10,595	2,195	2,088	46	28	14	0	6	0
Itaux	7,341	6,172	1,399	1,201	28	11	6	1	5	0
Brooklyn	14,333	12,162	2,260	2,161	43	30	7	3	9	0
Queens	6,829	5,952	1,142	1,177	12	18	2	1	4	2
Richmond	1,379	867	211	141	3	1	0	1	1	0
	43,978	35,748	7,207	6,771	132	83	29	6	25	2
TOTALS	79,726		13,978		220		35		27	

nant varieties; endothelioma (Ewing's sarcoma) is next, followed by plasma cell myeloma, reticulum cell sarcoma, liposarcoma, and the rare forms of myeloma, such as erythroblastoma and myelocytoma. The latter two tumors are exceedingly rare.

Metastatic tumors, however, are encountered more often. While nearly every form of carcinoma has been known to produce bone metastasis, there are several that are particularly prone to do so, *i.e.*, mammary, renal, thyroid, and prostatic. Less commonly seen are bronchiogenic carcinoma and adenoid cystic epithelioma of basal-cell type originating in the oral cavity. Hodgkin's disease and endothelioma of bone also frequently produce bone metastasis. The relative frequency is noted in Table IV which comprises 912 consecutive cases of benign and primary malignant tumors of bone on record in the files of Memorial Hospital. The preponderance of osteogenic sarcoma among the malignant tumors and of giant cell tumor among the benign ones is clearly demonstrated. The table does not include metastatic lesions of bone which group constitutes the most numerically important of all.

SEX

The influence of sex on the incidence of bone tumors is not striking. Most writers find a slight preponderance of the male sex. No endocrinologic explanation has been suggested. The possibility of more frequent and more pronounced injuries in the male is obvious, but that it is a causative factor is not readily established; many discount the part played by local trauma.

NEOPLASMS OF BONE

TABLE IV

INCIDENCE OF BONE TUMORS*

PRIMARY MALIGNANT		CASES	PERCENTAGE
Osteogenic sarcoma (including chondrosarcoma and malignant giant cell tumor)		392	66
Endothelioma (including angiosarcoma)		131	22
Myeloma		53	9
Lymphosarcoma (including reticulum cell sarcoma)		10	3
Liposarcoma		6	1
Total Malignant		592	
BENIGN			
Giant cell tumor		140	44
Bone cyst		48	15
Angioma		9	3
Cartilage tumors: Osteochondroma		74	23
Chondroma		33	10
Dyschondroplasia		16	5
Total Benign		320	

* Memorial Hospital as of January 1, 1940

AGE

The age of the patient is of importance since different types of tumors occur in different age groups. Osteogenic sarcoma is primarily a disease of childhood, youth, and early adult life although it may occur at any age. Ewing's sarcoma, or endothelioma, also affects persons in these age groups but is seen only rarely after the age of 25. Tumors diagnosed as *endothelioma* in middle life are usually examples of reticulum cell sarcoma. Giant cell tumor is essentially a disease of early adult life, the period of greatest frequency occurring between 21 and 35; cases having their onset after the age of 45 are rare. Plasma cell myeloma, on the other hand, attacks those past 40 and is most frequent in the decades from 50 to 70. Bone cyst is found during the actively growing period of childhood, seldom manifesting itself after the epiphyses have closed. Metastatic tumors of bone form the largest group that affect those past middle life and follow the age common to the primary carcinoma from which they originate. For further details see the chapter on "Differential Diagnosis," pages 41-50.

2. ETIOLOGY

IN GENERAL, LITTLE CAN BE SAID CONCERNING THE EXACT CAUSE OF BONE tumors; this is a matter that is still largely conjectural. It is probably safe to assume, however, that different etiologic factors are concerned in different varieties of bone tumors rather than to ascribe all types to the same factor or factors. It is our belief that a combination of several different factors is requisite for the development of primary malignant tumors of bone and that the existence of the factors singly, without the combination, is not followed by tumor development. Of course we do not know as yet what these factors are.

TRAUMA

It seems inescapable to the clinician, if not to the pathologist, that there is more than coincidental relationship of preexisting injury to bone tumor development, yet none can deny that injuries comparable in severity are sustained by nearly everyone while the incidence of "bone cancer" in the United States registration area for several successive years has only been about 1.5 per 100,000. Therefore trauma cannot be the sole causative factor.

The weight of medical opinion is certainly against the theory that mechanical trauma is an important factor in the causation of malignant tumors. By *trauma* is meant a single or repeated contusing, crushing, or lacerating injury. Roger Williams, Roussy, Lubarsch, Knox, Ewing, and Stewart are among those who contend that normal tissues do not react to a single trauma by malignant proliferation. For further discussion see page 726.

CELL REST THEORY (COHNHEIM)

This theory presupposes a congenital misplacement of embryonal cells that remain quiescent until, due to some inciting factor at a later date, they begin to take on unrestrained cell growth and become truly malignant tumors. This theory may be a factor in some varieties of bone tumor, notably certain chondromas and chondrosarcomas. It is difficult to conceive of it, however, as being the explanation of the origin of the majority of malignant bone tumors.

INFECTION

The theorist must proceed cautiously before discarding infection as a causative factor in the development of bone tumors. Certain forms, such as endothelioma, might possibly result from a chronic or subacute attenuated bone infection that usually does not go on to actual suppuration. The stimulation afforded to cells composing bone by the presence of certain inflammatory processes may be the method by which infection acts to incite tumor formation. It is possible that in the case of certain tumors, such as endothelioma, further bacteriologic investigation may disclose an association with some organism which causes an intense local stimulation of bone tissue without producing frank suppuration. Certainly endothelioma of bone has many clinical features and roentgenographic findings that closely resemble certain known infectious diseases of bone.

Space will not permit of a detailed account of the historical background of the *infectious theory* of malignant growths. Suffice it to say that from the time of Paget up to the present there have been distinguished investigators who have maintained that there is some relationship between microorganisms and malignant disease. Among the staunchest proponents of this concept was William B. Coley, who, while lacking the support of many of his contemporaries, steadfastly held to his views on the subject.

HEREDITARY PREDISPOSITION

Here again we are ignorant of the role played by heredity and yet it may well be one of the factors concerned. The instance of three siblings developing osteogenic sarcoma would suggest it, for on the basis of chance the odds against such a coincidence would be tremendous (see Fig. 144, p. 272). Hereditary influence in multiple osteochondroma has been discussed in detail by Jaffe and others. Familial chondrodysplasia is well recognized. Certain tumors arising in preexisting normal cartilage may have an important hereditary background. Thus far, however, any relationship of heredity to the development of bone sarcoma must be regarded as lacking in scientific proof.

VITAMIN DEFICIENCY

This is another factor that may conceivably produce so as to render it more favorable for the development of and rachitic changes are among those suggested. Vitamin chemical or laboratory, has been shown to elaborate factors. It would seem a reasonable assumption that might be made. Yet we have not found any of bone clinical manifestations of vitamin deficiency; on the

marked that these diseases seemed to attack otherwise healthy and well-developed individuals.

Recent research and particularly animal experimentation have shown that biotin, a member of the B vitamin complex and one distributed widely in human and animal tissues, influences the development of experimentally produced cancer of the liver in animals. This investigation may have an important bearing on the general subject of vitamins and cancer. Further study along these and similar lines will unquestionably be forthcoming.

ENDOCRINE DISTURBANCES

Though endocrine dysfunction, particularly involving sex hormones, has been shown to be related closely to the development of certain malignant tumors, no such connection with tumors of bone origin has been established. Additional research along this line might yield information of importance. For example, fibrous dysplasia, associated with pigmentation and sexual precocity in females, has been described by Albright and also by Jaffe. While they do not mention malignant bone changes in areas of dysplasia or cystic osteitis, several examples of such changes have been observed in Memorial Hospital. The underlying bone disease seems inherently associated with some endocrine abnormality.

3. DIAGNOSTIC SURVEY IN SUSPECTED CASES OF TUMOR OF BONE

WHENEVER A CASE IS ENCOUNTERED WHICH LEADS ONE TO SUSPECT THE presence of bone tumor, immediate steps should be taken to confirm or disprove the suspicion. Carelessness or indifference on the part of the patient as well as the physician are often responsible for the delay in arriving at a diagnosis. Too often the patient is dilatory about seeking medical advice. When he does, the doctor too often takes but a superficial history, makes a cursory examination, and proceeds to reassure the patient that nothing serious exists; only local measures are prescribed, such as liniments, baking, and massage. Our records show that usually a long period elapses between the first symptom and the arrival at a correct diagnosis.

HISTORY

Of first importance is an accurate history. When carefully elicited it becomes a valuable part of the record and is an indispensable link in the diagnostic chain. An effort should be made to list the symptoms in chronologic order, stressing accuracy as to their sequence and time intervals.

PRESENT ILLNESS

Pain

This is nearly always the first symptom of a malignant tumor. Generally its onset is insidious. At first it is of mild degree and often intermittent. Soon its character changes and it becomes steadily and progressively more severe. Ultimately it becomes almost intolerable, interferes with sleep and requires medication for a relief which is only temporary. It is generally worse at night although an exception is the pain in multiple myeloma which is usually relieved by bed rest and consequently is often diminished or absent at night. The pain is usually complained of at or near the site of the tumor, although in the early stages this may not be apparent by inspection or even by palpation. Sometimes the pain is referred to a point distant from the actual site of the tumor, such as the sciatic distribution of pain

in cases primary in the ilium or sacrum. Upon the symptom of *pain* alone one should be prepared to make a presumptive diagnosis of sarcoma of bone and to proceed by roentgenographic and other measures to confirm or exclude it.

Trauma

The history should record any incidence of recent injury or infection. If there has been a previous trauma, its site, severity, and subsequent evidence of injury to bone or overlying tissues (swelling, ecchymosis, tenderness) should be recorded. The time of its occurrence may have an important bearing on any future medicolegal aspects of the case. Likewise the interval between the subsidence of the immediate symptoms and the development of those referable to the presence of the tumor is of great importance and should be carefully noted. Trauma may often call the patient's attention to a tumor which was already present.

Swelling

This symptom is next in importance. It is usually noticed after the pain has existed for some time. Its recognition is earlier in bones sparsely covered with muscles than in those deeply seated, such as the pelvis. It is also manifest earlier in tumors that occur in the periosteal or subperiosteal area than in those originating in the medullary portion of the bone. In metastatic disease it is frequently absent entirely. A history of sudden increase in size of a tumor long known to have been present, but symptomless and quiescent, is strongly suggestive of a malignant transformation of a benign osteochondroma.

Disability

As a result of pain and swelling, disability is often noted only late in the course of the disease. Great variation exists in the degree of functional impairment. It is usually more pronounced in rapidly growing malignant tumors; it may be entirely lacking in certain benign conditions, e.g., bone cyst and osteochondroma. Since many primary tumors occur near a joint, it is the function of this joint that becomes impaired; therefore, in the lower extremity lameness is usually an early manifestation.

PAST HISTORY

It is well to record the facts regarding previous illnesses and particularly those which may give rise to bone lesions, e.g., syphilis, osteomyelitis, typhoid fever, tuberculosis, thyroid operations, and previously treated malignant disease of any organ or system.

Syphilis is able to produce lesions in bone that may mimic nearly all forms of benign and malignant tumors of bone. Tuberculosis may rarely affect the bone at a distance from joint surfaces and give rise to osteolytic

areas that might be considered as metastatic cancer or even a primary bone sarcoma such as reticulum cell sarcoma. We have seen cases of plasma cell myeloma of the vertebral bodies for which spine fusion had been performed in the belief that Pott's disease existed.

Bone abscess may resemble central chondrosarcoma of low grade character. Foci of metastatic thyroid carcinoma of the variety often called "benign metastasizing struma" may be noted as long as ten or twelve years after a thyroidectomy for what was considered histologically to be a benign goiter. Less frequently one encounters metastatic bone cancer at long intervals following operation and apparent cure of other forms of malignant disease. Such examples should demonstrate the desirability of eliciting a careful history of past illnesses.

PHYSICAL EXAMINATION

A complete physical examination is essential. It may reveal an unsuspected primary tumor (the bone lesion being metastatic) or the presence of venous implants in the femoral or iliac region from a sarcoma of the tibia or lower femur. This need for examination increases after middle life since the incidence of visceral carcinoma as a cause of metastatic osseous lesions greatly outnumbers primary sarcoma.

Inspection of the local area should reveal swelling, changes in the color of the skin, and dilatation of superficial veins.

Palpation gives information as to the extent and general outline of the tumor and its consistence. Movability over the bone indicates a soft-tissue tumor rather than a bone tumor. Pulsation is rare; when present it indicates an extremely vascular tumor; in central tumors it indicates a destruction of a portion of the cortex.

The consistency of the tumor is to be noted. In rapidly growing, highly malignant tumors it is not bony but may be rubbery, hard, or elastic.

In the early stages the skin is normal and not adherent to the underlying tumor; in the later stages it becomes thin, with prominent superficial veins, and palpation will disclose that the skin is relatively adherent to the underlying tumor.

Measurements of the affected and the normal limb should be made at comparable levels and recorded on the chart. The degree of impairment of movements of the joint adjacent to the tumor should also be noted.

Pulsation, while in our experience a most unusual finding in bone tumors, does occur in certain osteolytic metastatic lesions due to thyroid or renal cancer; it is noted infrequently in telangiectatic osteogenic sarcoma (malignant bone aneurysm) and only rarely in benign giant cell tumor of bone.

Codman's theory of the mechanism of a giant cell tumor (see p. 170) explains pulsation. Yet in 1946 Shallow and Wagner found only 7 instances of pulsating giant cell tumor in the literature from 1900 to the present

time. Their own case apparently did not show pulsation until after the first operation.

The reason why pulsation is noted so seldom is that two factors must be present before it is detectable: (1) the cortical shell must be destroyed on the surface of the tumor; and (2) the artery which enters the tumor must be of sufficient caliber to make a pulsation perceptible. Since intra-tumoral clotting and organization of the resulting clot probably takes place in most cases the pulsation tends to be muffled and diminished as far as perception is concerned.

These tumors have been reported by Bloodgood, Morton and Duffy, Lewis, Mider and Morton, Scott, and Shallow and Wagner. We find no examples of pulsation in any of our untreated cases of giant cell tumor. It is not a finding of great diagnostic importance. Microscopic study of these cases has failed to incriminate the process as malignant and the histologic picture may not differ in any respect from a nonpulsating tumor; nor has late malignant degeneration complicated any of the cases thus far reported. However, they are unquestionably more aggressive and less consistently cured by curettage. In 3 of the 7 cases amputation of the limb was ultimately required. The prognosis as to limb must be guarded. The prognosis for life is that of the usual giant cell tumor, but one should not lose sight of the fact that it is less readily controlled by treatment and there is an increased likelihood of late malignant degeneration which appears to be associated with repeated recurrences following either surgical or roentgen therapy.

ROENTGENOGRAPHIC EXAMINATION

It is difficult to overemphasize the importance of an adequate roentgenographic examination. A skillful interpretation of the films will afford very valuable information from which a presumptive diagnosis—a correct one in a high percentage of cases—can usually be made. With the possible exception of the histologic examination it is the most important step in the diagnostic survey and should be insisted upon by the physician who first sees a case of suspected tumor of bone. This is the greatest contribution he can make toward the early establishment of the diagnosis. ✓

The films should include a large area adjacent to that in which the patient complains of pain. Failure to do so may occasionally result in negative findings with consequent delay in establishing the correct diagnosis because the diseased area of bone may be some distance from the point of maximal pain. For example, a case of endothelioma of the middle third of the femur was unsuspected for several months after a small-sized film of the knee failed to reveal anything abnormal when the chief complaint was "pain in the knee." Had a 10" x 12" film been taken at the first examination some of the affected bone would have been seen and

the diagnosis would then have been established months earlier. Numerous other examples could be cited in which an incomplete or inadequate examination was made with similar results.

In addition to single exposures, stereoscopic views are frequently of great value. As an illustration, a case of myositis ossificans had been considered, on a single film, to be osteogenic sarcoma and in this instance the report of an open biopsy had confirmed this opinion. Stereoscopic films were then made, fortunately, and the process was seen not to involve the bone at all but to be entirely in the soft tissue surrounding it. Thus, by a narrow margin, the patient was spared an amputation at the shoulder joint.

Stereoscopic views in another case involving an osteogenic sarcoma of the femur showed what single views had failed utterly to demonstrate, namely, that the tumor developed in a somewhat sessile osteochondroma of the lower femur. As a result, a resection of the entire growth was done with saucerization of the base of the tumor where it arose from the femur. This patient has remained well and the functional result has been excellent for ten years (see Fig. 155, p. 285). Amputation would most certainly have been considered advisable unless stereoscopic films had supplemented ordinary anteroposterior and lateral views. Tomographic examination may be of assistance in rare instances, particularly in skull and spine lesions where overlapping of normal bone makes interpretation more difficult.

It is also considered desirable to make an oblique exposure as well as the conventional anteroposterior and lateral for it may yield additional information. Films of the comparable bone of the unaffected side should be made for comparison.

Information obtained from studies of the chemical constituents of the blood may point to the necessity for securing films of the entire skeleton; e.g., if a high serum calcium and slightly elevated serum phosphatase are found, the suspected single lesion may be only one of a number of involved areas in the generalized form of cystic disease seen in hyperparathyroidism.

Some roentgenologists routinely make exposures of cases of suspected bone disease so as to bring out soft tissue detail as well. While this may be worthwhile, if a bone tumor is found to be present or if it is suspected, then other films should be made with longer exposure for better bone detail. The ideal examination should include:

1. Scout exposures made on large films in at least three planes
2. Stereoscopic views and views made to bring out varying degrees of tissue density, if a lesion is found that is suspicious of a tumor of bone
3. Chest films in two planes (anteroposterior and lateral)
4. Views of other bones or entire skeleton, if indicated

In the event of any bone pathology being disclosed, a chest film should be made before a decision as to treatment is reached. Examination of the chest should include a lateral as well as the usual anteroposterior view. Only thus may one avoid overlooking a metastatic nodule lying behind the cardiac shadow.

As a result of roentgenographic examination, the bone lesion can often be classified not only as a tumor but as one of benign or malignant character, and even its exact nature may be diagnosed. Caution is necessary, however, for the roentgenographic features of the various bone tumors closely simulate each other and there may be a 15- or 20-per cent error when the diagnosis is later checked by microscopic examination.

PSEUDOCYSTIC LESIONS OF BONE

In interpreting films made of bone conditions one of the most commonly seen abnormalities involves skeletal defects due to radiolucent areas caused by replacement of normal bone fabric by tumor, connective tissue, abnormal metabolic products, or cells of benign neoplasms, such as chondroma, adamantinoma, etc. The following conditions may give rise to lesions which can be termed *pseudocystic*:

Generally Single

1. Brodie's abscess
2. Nonosteogenic fibroma
3. Eosinophilic granuloma
4. Adamantinoma
5. Central chondroma
6. Giant cell tumor

Generally Multiple

1. Hyperparathyroidism
2. Osteitis deformans
3. Metastatic carcinoma
4. Myeloma
5. Fibrous dysplasia
6. Hand-Schüller-Christian's disease
7. Gaucher's disease
8. Essential xanthomatosis

Some of the conditions which give rise to the greatest difficulties from a purely roentgenographic standpoint are considered under "Differential Diagnosis."

LABORATORY STUDIES

In addition to a complete blood count, a serologic examination of the serum calcium, phosphorus, and phosphatase is essential. Of these, the latter is most frequently altered in the presence of certain metastatic and primary bone tumors. Taken in conjunction with other factors, especially the roentgenographic findings and the age of the patient, the serum phosphatase level may be diagnostic.

From extensive investigations carried out in the Biochemistry Department of Memorial Hospital, Woodard, working with the clinicians in the Bone Tumor Department, has drawn the following conclusions:¹

¹WOODARD, HELEN Q., and HIGINBOTHAM, N. L. The correlation between serum phosphatase and roentgenographic type in bone disease. *Am. J. Cancer* 31:236, 1937.

1. If a high serum phosphatase is found associated with an osteoplastic lesion or a normal serum phosphatase with an osteolytic lesion, then the phosphatase determination has served only to confirm the diagnosis made by roentgenograms.

2. If a normal serum phosphatase is found associated with an osteoplastic lesion, the process is probably slow-growing and relatively benign.

3. If a high serum phosphatase is found associated with an osteolytic lesion, several possibilities present themselves:

(a) The case may be one of hyperparathyroidism. If this is so, the serum calcium and inorganic phosphorus will nearly always be abnormal and will serve to establish the diagnosis.

(b) There may be osteoplastic disease elsewhere in the body which will account for the high serum phosphatase, even though the presenting lesion is osteolytic.

(c) The case may be one of a group made up chiefly of endotheliomas or carcinomas of diverse origin, metastatic to bone, which raise the serum phosphatase level, but for some unknown reason do not form new bone. The presence of an elevated serum phosphatase may serve to distinguish these lesions from various types of benign osteolytic disease, which very seldom raise the serum phosphatase.

(d) The case may be an early highly malignant osteogenic sarcoma. Some of these fail to show new bone formation, probably because their very rapid growth-rate outstrips the relatively slow deposition of calcium phosphate. Such tumors may show osteoplasia later in the course of the disease. In these cases the association of a high serum phosphatase with a rapidly growing osteolytic lesion probably indicates a high degree of malignancy.

4. Follow-up determinations of the serum phosphatase in cases with an initially elevated phosphatase may predict the development of metastases after the extirpation of the primary tumor, but cannot be depended on to do so.

5. Determinations of serum phosphatase in cases of bone tumors which have been treated by roentgen or gamma rays are useful in indicating the degree and permanence of the inactivation caused by irradiation.

6. Finally, we feel that, while the presence of a normal serum phosphatase gives no assurance that bone disease is absent, the presence of a persistently elevated serum phosphatase in a patient who is not jaundiced and who is not under treatment with Coley's toxins is a very strong indication that bone disease is present and should never be disregarded.

For a complete consideration of the chemical constituents of the blood in bone disease, see Chapter 5, pages 51-68.

BIOPSY

This is part of the management of a case of osteogenic sarcoma which should be the responsibility of the surgeon who is prepared to carry out later treatment. Ill-advised and improperly performed biopsy may, and frequently does, reduce the patient's chance of cure to zero.

SURGICAL BIOPSY

Surgical biopsy is an extremely important method of diagnosis. It should always be regarded as an operation of major importance and not a minor

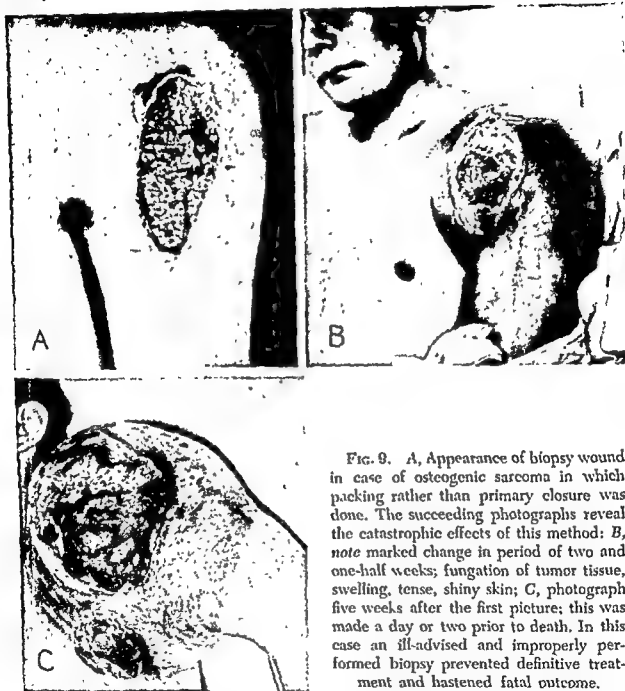


FIG. 9. A, Appearance of biopsy wound in case of osteogenic sarcoma in which packing rather than primary closure was done. The succeeding photographs reveal the catastrophic effects of this method; B, note marked change in period of two and one-half weeks; fungation of tumor tissue, swelling, tense, shiny skin; C, photograph five weeks after the first picture; this was made a day or two prior to death. In this case an ill-advised and improperly performed biopsy prevented definitive treatment and hastened fatal outcome.

procedure involving little risk, requiring no special skill, and capable of being performed by any surgeon who just happens to see the case. It should be the final step in the investigation of a suspected case of bone tumor. A careful history, complete examination, laboratory studies including blood chemistry, and a thorough roentgenographic examination will yield a correct diagnosis in a large majority of cases. To rely on a hasty biopsy tends to establish habits of carelessness in collecting clinical data and reviewing roentgen findings. Moreover, the pathologist is placed at a

disadvantage when he is asked to make a diagnosis where clinical and roentgenographic data are lacking.

The undesirable complications of a biopsy can be largely avoided, but to do so requires experience, judgment, and a knowledge of technic; therefore it is desirable to defer biopsy until it can be performed by the surgeon who will have full responsibility for future care of the patient.

Ill-advised or poorly performed surgical biopsy can disseminate disease, cause fungation of the tumor through the incision, add to the hopelessness of the situation, and cause much discomfort to the patient (see Fig. 9). When the operator encounters alarming hemorrhage in a situation which is not susceptible of control by tourniquet the employment of oxidized gauze or fibrin foam to pack the cavity, followed by layer-closure, is an exceedingly valuable expedient and is certainly preferable to draining or packing the wound without complete closure.

Biopsy should precede any mutilating operation such as amputation. It can be performed under a tourniquet with preparation made to amputate at once if the pathologist decides on frozen section that the tumor is malignant. While waiting for the report, the incision is closed and the field is redraped. Fresh instruments are provided and the operating team changes gloves. Meanwhile, the tourniquet remains in place. This method avoids the likelihood of dissemination of tumor cells, but its principal limitation lies in the inability of the pathologist in some instances to make satisfactory frozen sections because of the presence of bony tissue or calcified material; such a specimen requires decalcification and paraffin sections. In these cases the operator may rarely have to defer amputation for several days until positive assurances can be had. Only by constantly observing these precautions can he be certain that he is not amputating for a benign bone lesion.

Technic of Surgical Biopsy

The following points should be observed meticulously:

1. Skin preparation must be as careful and thorough as though a bone graft or bone plating were contemplated.
2. Incision must be clean, and tissue trauma and rough handling reduced to a minimum.
3. Specimens should be removed from the periosteum and underlying cortical bone and from the medulla, using great care to select the optimum site for approach after study of stereoscopic roentgenographs. The site of removal of tumor tissue may be swabbed with saturated solution of zinc chloride, avoiding the soft tissues and skin edges.
4. Hemostasis must be accurate, but under no condition should oozing from the tumor tissue bed prompt the surgeon to use drainage or packing.

5. Wound closure should be in layers. Fine, nonabsorbable suture material, such as cotton, is preferable. Snugly fitting, compressible dressings should be applied. For this purpose, cotton waste or sheet wadding is useful.

6. Skin sutures should be removed early, but it is essential to support the line of incision with strips of flamed adhesive until the skin is firmly healed. A separation of the wound edges may have serious implications.

ASPIRATION BIOPSY

Up to about fifteen years ago, operative biopsy by direct surgical approach was the method by which specimens of tumors lying beneath the skin or mucous membrane were obtained. This method is still the most widely used and has certain definite advantages which will be mentioned later.

It would appear that Micotti's case (1922), in which a diagnosis of chordoma was made when he inadvertently obtained a small piece of tissue while aspirating what he believed to be a cyst, represents the first recorded example of a successful aspiration biopsy.

Aspiration biopsy was described by Martin and Ellis in 1930. It has been continuously employed since then at Memorial Hospital and has now been adopted in many other clinics in the United States and abroad. Their results show that material thus obtained has been satisfactory for histologic study and that the information gained has been of great value in establishing a diagnosis.

Advantages and Disadvantages of Aspiration Biopsy

The advantages we may mention are: the simplicity of the technic of obtaining the material for study; the fact that it can be carried out in the outpatient or examining department with little inconvenience to the patient; that it permits of immediate operation or radiation therapy without the lapse of time necessary for wound healing as is the case when a formal biopsy is performed; and finally, that it obviates hospitalization and consequent expense to the patient.

Certain theoretical disadvantages may be claimed for this method. For example, in some cases no tissue is obtained at aspiration; in others, tissue cells are obtained but they cannot be identified as tumor cells. The possibility must be kept in mind that viable tumor cells may be implanted along the needle tract or, in the case of vascular tumors, intratumoral hemorrhage may result, affording the opportunity for tumor cells to become dislodged into the blood stream and cause distant metastasis.

We have not seen any instances of tumor implantation along the tract of the needle or of dissemination of the tumor that could be attributed to the aspiration.

thumb about which we were most uncertain from clinical and roentgenographic examinations.

Aspiration is adaptable to all types of bone tumors except those in which the tumor is deeply situated and surrounded by a zone of normal bone through which the needle cannot be made to penetrate. Fortunately the majority of such tumors are susceptible of diagnosis without biopsy (most frequent examples of this type are giant cell tumor, benign cyst, etc.). In a doubtful case the surgeon should resort to an operative biopsy.

For those unfamiliar with the actual technic, we quote the following:²

The special paraphernalia required is an ordinary 18-gauge needle 5 to 10 cm. in length (which should be new and sharp) and a 20 cc. Record syringe. For the preservation of the specimen, glass slides and a specimen bottle with 10 per cent formalin are needed (see Fig. 10).

The skin at the site of the intended puncture is painted with iodine and a small area of skin infiltrated with 1 per cent solution of novocaine. With a bistoury pointed scalpel (No. 11 Bard Parker blade) a minute stab wound is made through the skin with the instrument held at right angles to the skin surface. This puncture of the skin facilitates insertion of the needle. An 18-gauge needle attached to a tightly fitting Record syringe is then inserted and advanced slowly through the superficial tissues until the point is felt to enter the suspected neoplastic mass. Guided by palpation with the disengaged hand, it is striking how readily a difference in consistence of the tissues can be felt as the needle enters a mass of neoplasm. When the point of the needle is felt to enter the tumor, the piston of the syringe is partly withdrawn so as to produce a vacuum and the needle slowly advanced 1 to 3 cm., depending on the anatomy and size of the tumor. Maintaining the vacuum, the needle is then withdrawn to the same distance and advanced again. This manipulation may be repeated two or three times at the discretion of the operator, care being taken to maintain the vacuum when the needle is advanced or withdrawn. Aspiration with the needle at rest is not sufficient to draw tissue into the needle in most cases. By advancing the needle and aspirating simultaneously, a plug of tissue is both forced and drawn into the needle. Maintaining suction during partial withdrawal detaches the plug of tissue already within the needle. We have found this detail to be very essential. Before the needle is completely withdrawn from the tissue, the piston must be slowly released until the pressure in the needle is equalized, or better still, the syringe detached and the needle withdrawn separately, otherwise the aspirated material will be suddenly drawn and splashed over the interior of the syringe, making its collection difficult. While the needle is being advanced and withdrawn under negative pressure, a small quantity of blood mixed with fragments of tissue may enter the syringe or a solid cylindrical mass of tissue may appear. In other cases, especially in the firmer masses, the syringe apparently remains empty but, after withdrawal, the needle is usually found to contain a plug of tissue.

After complete withdrawal of the apparatus, the syringe is detached from the

² MARTIN, H. E., and ELLIS, E. B. Biopsy by needle puncture and aspiration. *Ann. Surg.* 92:171, 1930.

needle, filled with air, attached and the contents of the needle slowly and carefully expelled on a glass slide. A small fragment of tissue should be left on the slide for smearing and the remainder placed in the specimen bottle for fixation and staining

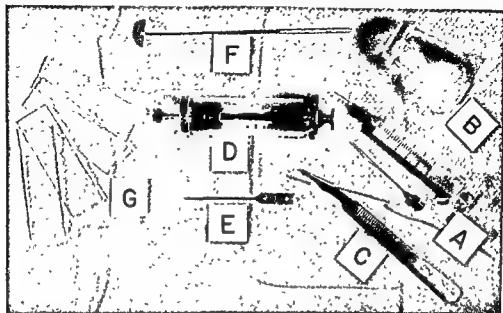


FIG. 10. Aspiration biopsy set. A, 12 cc. hypodermic syringe with short and long needles for novocaine infiltration; B, sterile medicine glass for novocaine solution; C, scalpel with #11 Bard Parker blade; D, 20 cc. Record syringe; E, 18 gauge needle with obturator; F, instrument for raking out tissue from barrel of syringe; G, glass slides for smears of aspirated material.

by regular methods. If the needle is empty, small masses of tissue can almost always be found mixed with blood in the syringe and these should, if necessary, be very carefully searched for. One or two of these small masses can readily be fished out upon a glass slide for smearing and immediate staining. In any case where the syringe contains blood or any tissue, formalin from the specimen bottle is poured into the open barrel of the syringe, agitated and returned to the specimen bottle.

PREPARATION OF THE SPECIMEN

There are two methods—the shorter requires about 20 minutes, the longer about 2 hours. If time permits, the longer method has the advantages of providing a fixed, cleared preparation.

The Shorter Method

The fresh tissue fragment on the glass slide is smeared by very firm flat pressure by another glass slide drawn once across. The smeared slide is fixed by heating gently over a gas flame until warm and dry, and is then prepared according to the following technic:

- | | |
|--------------------------------|-----------|
| 1. Xylol | 2 minutes |
| 2. 1st dioxan (or 95% alcohol) | 1 minute |
| 3. 2nd dioxan (or 95% alcohol) | 1 minute |
| 4. 95% alcohol | 1 minute |

- | | |
|---|----------------|
| 5. 80% alcohol | 1 minute |
| 6. Water | 1 minute |
| 7. Hematoxylin | 1 to 2 minutes |
| 8. Thorough wash in water. Ammonia or lithium carbonate may be added if desired, followed by rinse in tap water | |
| 9. Eosin, aqueous or alcoholic | 1 to 2 minutes |
| 10. 80% alcohol | 1 minute |
| 11. 95% alcohol | 1 minute |
| 12. 1st dioxan | 1 minute |
| 13. 2nd dioxan | 1 minute |
| 14. 1st xylol | 1 minute |
| 15. 2nd xylol | 1 minute |
| 16. Mount in gum dammar or other suitable medium | |

The Longer Method

The remainder of the specimen is handled as any other small biopsy specimen. It is embedded in paraffin, taking pains to collect every minute particle of tissue.

If a more rapid reading is essential than can be had by the routine method, we may use the following method of preparation which requires less than three hours.

The Quick Paraffin Method

- | | |
|--------------------------------------|------------------|
| 1. Formalin, 10% | 10 to 15 minutes |
| 2. 1st dioxan | 10 minutes |
| 3. 2nd dioxan | 10 minutes |
| 4. $\frac{1}{2}$ dioxan and paraffin | 10 minutes |
| 5. 1st paraffin | 15 minutes |
| 6. 2nd paraffin | 30 minutes |

(First 4 steps in oven at 37° C.

Last two steps in oven at about 56° C.)

7. Cut, mount, and stain

Biopsy by this method has advantages which are considerable. It can, if unsuccessful, be at once followed by operative biopsy. Undoubtedly it will never be a substitute for the latter under all conditions and will not entirely displace it. It has inherent dangers which should not be disregarded; namely, the possibilities of grave error and consequent ill-advised radical surgery. This is likely to occur when the diagnosis is based on aspirated material seen by a pathologist inexperienced in interpreting it. The heavy responsibility which this method places upon the pathologist is perhaps the strongest reason for its limited field of usefulness. Another and more theoretical objection is the possible tendency of a tumor that has been needled to disseminate cells to distant parts as a result of intratumoral hemorrhage. This tendency should be more marked when vascular growths

(telangiectatic osteogenic sarcoma, Ewing's sarcoma) are aspirated than when it is used for more fibrous or fleshy tumors.

DIAGNOSTIC RESULTS OF ASPIRATION BIOPSY

In a recent communication, Snyder and the author reported a series of 568 aspirations in 474 individuals with tumors or other conditions involving the skeleton, excluding the head and jaw regions (see Table V). This series represents the experience of the Bone Tumor Department of Memorial Hospital during the past fifteen years. A careful analysis reveals that there were no immediate complications, no late sequelae, nor any evidence to suggest that this diagnostic procedure had encouraged the development of metastasis.

A study of the groups included in this series shows the following:

Osteogenic Sarcoma

This classification included all types of osteogenic sarcoma and chondrosarcoma and comprised the largest group (132 cases) submitted to aspiration biopsy. Of these 67, or 53 per cent, were classified as osteogenic sarcoma on smear or sectioned clot while an additional 34 were called malignant tumor, type not determined. Thus in 76 per cent a definite diagnosis of malignant tumor was made without resorting to a formal biopsy. Two were reported as benign tumors. One of these was a lesion of the ilium which was reported as "chondroma in this section but does not exclude sarcoma in other parts," and the patient subsequently died of pulmonary metastasis. The other was an unusual case of low-grade osteogenic sarcoma of the proximal phalanx of the fifth finger which was reported as "consistent with giant cell tumor." This patient, incidentally, is living and well without evidence of disease seven years after operation. In only 29 cases, 22 per cent, did aspiration fail to yield tissue or yield insufficient tissue for interpretation.

Endothelioma (Ewing's Sarcoma)

Of a total of 42 cases, 31 had positive aspirations; 6 were diagnosed as malignant tumors impossible to classify or differentiate from osteogenic sarcoma. This is significant in view of the fact that endothelioma and osteogenic sarcoma are often difficult or impossible to differentiate on the basis of roentgenographic appearance. Only 5 failed to yield diagnostic material, making a positive percentage of 89. It is interesting to note that 2 of these cases had had previous open biopsies early in their course which showed only chronic osteitis in the tissue obtained. Both died shortly of multiple lesions. In each of these cases small doses of X-rays had been administered prior to the biopsy. This is contrary to our practice. We feel that the diagnosis should be established before any treatment is begun, as even a single

TABLE V
ANALYSIS OF ASPIRATION BIOPSY OF BONE LESIONS AT MEMORIAL HOSPITAL

DIAGNOSIS	TOTAL CASES	ASPIRATION DIAGNOSIS	TISSUE OBTAINED NOT SPECIFIC	SATISFACTORY ASPIRATIONS	MALIGNANT CALLED BENIGN	BENIGN CALLED MALIGNANT	ASPIRATION INSUFFICIENT FOR DIAGNOSIS	REPEAT ASPIRATIONS
<i>Primary malignant</i>								
Osteogenic sarcoma—all histologic types	132	67	34	101	2	0	29	27
Endothelioma	42	31	6	38	0	0	5	6
(Ewing's sarcoma)	38	26	3	29	2	0	7	9
Myeloma—all types	4	3	1	4	0	0	0	1
Reticulum cell sarcoma of bone	1	0	1	1	0	0	0	0
Liposarcoma	1	1	1	1	0	0	0	0
Angiosarcoma	4	1	2	3	0	0	1	1
<i>Metastatic</i>								
Metastatic carcinoma in os	107	90	4	94	0	0	13	25
Hodgkin's disease	3	0	1	1	0	0	2	1
<i>Miscellaneous tumors—malignant</i>	15	8	3	11	1	0	4	6
<i>Miscellaneous tumors—benign</i>	18	9	1	10	0	1	7	3
<i>Giant cell tumor</i>	30	23	3	26	0	0	4	4
<i>Bone cysts</i>	7	0	4	4	0	0	3	0
<i>Miscellaneous bone conditions</i>								
Paget's disease	6	1	0	1	0	0	5	0
Lipoid histiocytosis	4	2	1	3	0	0	1	2
Inflammatory diseases	45	7	16	23	0	0	22	9
Unclassified—benign	18	0	0	0	0	0	18	0
Total Repeat Aspirations	474	268	80	319	5	1	121	94
TOTAL ASPIRATIONS	568							

exposure may mask a tissue diagnosis of endothelioma with false reassurance and a prolonged delay in arriving at the correct diagnosis.

Reticulum Cell Sarcoma of Bone

The clot obtained by aspiration in 3 cases was diagnosed by Stewart as primary reticulum cell sarcoma. A fourth was called malignant tumor and proved to be reticulum cell sarcoma at operation.

Liposarcoma

One case had been classified as liposarcoma on the basis of open biopsy which was called spindle cell sarcoma at aspiration. An exact cell-type diagnosis could not be expected from an aspiration biopsy.

Giant Cell Tumor

Of 30 giant cell tumors of bone aspirated, 23, or 76 per cent, were diagnosed as giant cell tumor. One of these was regarded as malignant and proved to be so at operation. Two others showed malignant recurrence but aspirations were not diagnostic. In several cases the course of the disease during treatment was followed by means of aspiration biopsy specimens. This method may not be successful in cases of giant cell tumor because the intact cortex may act as a barrier to the needle.

Metastatic Carcinoma

Our second largest group aspirated was metastatic carcinoma (107 cases). During the course of a year many metastatic lesions of bone are encountered. In the majority the probable primary lesion is known. Aspiration biopsy is not a routine when the primary source of metastasis is obvious, but there are frequent instances of bone involvement with no such definite indication. Here a differential diagnosis must be made between metastatic carcinoma and primary bone tumor, or occasionally an inflammatory lesion. In most cases there is involvement of ribs, vertebrae, or pelvic bones. Any surgical procedure can be justified only for diagnosis; aspiration biopsy has, therefore, proved itself to be of distinct value. In the 107 cases aspirated, the biopsy was positive for metastasis in 90, or 84 per cent. In 4 additional cases, "malignant tumor unclassified" was reported, making 88 per cent satisfactory for a diagnosis of malignant tumor. In 25 instances the primary was suggested, and in many others the type of cell (adenocarcinoma, epidermoid carcinoma, etc.) was specified.

Hodgkin's Disease

Formal sections are considered necessary for a diagnosis of this type when it occurs in soft parts or in bone. Although not usually done, 3 cases were aspirated, 1 of which showed caseous granuloma.

Inflammatory Disease of Bone

A group of 45 patients with inflammatory disease of bone was aspirated, the diagnosis being based on a negative aspiration plus an open biopsy in some cases, the roentgenographic appearance, clinical course, and history. In 16 cases pus or granulations were obtained, and in 7 of 8 cases of tuberculosis the diagnosis was proved by aspiration. The aspiration was of value from a "negative" standpoint. In none of these cases was a false positive reported.

BENIGN TUMORS OF BONE

Most benign tumors are not suitable for aspiration biopsy and are not usually aspirated unless the roentgenographic picture is confusing. The material is frequently difficult to obtain and gives little information. Eighteen cases of chondroma, osteochondroma, chondromatous giant cell variant, and hemangioma were aspirated. Of these 8 were positive. One case was called chondrosarcoma of the distal end of the fibula but its roentgen appearance was that of a benign tumor; local resection showed only chondromyxoma. This is the only instance of a definite false positive, i.e., where a benign tumor was called malignant. It is of course well recognized by clinicians that failure to obtain tissue or material that is diagnostic does not mean that the lesion is not malignant unless all other factors are taken into consideration.

Bone Cysts

Cysts are unsatisfactory for aspiration and the procedure is usually not employed. Seven cysts were aspirated without positive findings except that fluid was obtained in a few instances.

Osteitis Deformans

This group also is not satisfactory for aspiration and the procedure is not recommended. Of 6 cases of Paget's disease that were aspirated, 1 yielded material consistent with this diagnosis.

Lipid Histiocytosis

Diseases of this type are occasionally seen and must be differentiated from tumor. One case of Hand-Schüller-Christian's disease and 1 of Niemann-Pick's disease with bone changes had the diagnosis established by aspiration. One case of eosinophilic granuloma was interpreted as a probable myeloma and a second case was not diagnostic.

Summary

A series of 568 aspiration biopsies of bone on 474 individuals have been studied and the results are tabulated in the accompanying table. There

were no immediate complications of the procedure and no evidence to suggest more rapid development of metastasis by the use of aspiration to establish the diagnosis. In primary bone tumors and metastatic carcinoma of bone, 385 cases were aspirated. Of these, 67.5 per cent were definitely and specifically diagnostic, while a total of 82 per cent showed material sufficient for the diagnosis of tumor, the exact type not being called in 14.5 per cent. In only 1 instance was a diagnosis of malignant tumor made when the resected specimen showed a benign tumor and in this case the treatment was local resection. Thus in no case was an unnecessary amputation performed because of erroneous diagnosis. Aspiration insufficient for diagnosis means only that no tissue was obtained, and its interpretation must be evaluated with the clinical and roentgenographic findings in mind.

BONE MARROW ASPIRATION

Sternal puncture has become an accepted means of obtaining smears of bone marrow. This procedure is particularly useful as a diagnostic measure in cases of suspected plasma cell myeloma as well as in leukemia and metastatic carcinoma.

ILIAC CREST VERSUS STERNAL MARROW ASPIRATION

Rubenstein has made a study of bone marrow obtained from aspirations simultaneously performed in both the sternum and the iliac crest in a series of approximately 200 cases of blood diseases and neoplasms. His conclusions are that iliac marrow aspirations are of greater value in the early diagnosis of myeloma than are sternal punctures because the percentage of cells typical of plasma cell myeloma is consistently higher in iliac marrow than in sternal marrow. This situation is true to an even greater degree in metastatic carcinoma. Rubenstein found that positive findings in the recovery of metastatic cells was ten times as great in iliac crest as in sternal aspiration, particularly when the primary growth was in the breast, lung, prostate, or kidney.

4. DIFFERENTIAL DIAGNOSIS

WHILE IN THE MAJORITY OF CASES OF TUMOR OF BONE A DEFINITE diagnosis can be made, in others it may be difficult to distinguish the various forms of malignant bone tumors from each other, from benign tumors, and from certain nonneoplastic diseases of the bone. The roentgenograms in many instances bear a close resemblance or may even be indistinguishable. Moreover, the variation in symptomatology, roentgenographic appearance, and clinical course that can be found among examples of one type of tumor (osteogenic sarcoma) adds to the difficulty. It may be said that there are insensible gradations from a benign to a highly malignant neoplasm.

The history is an important guide. Tumors that have been present for long periods, causing no symptoms, are usually benign. A sudden increase in size, following a long period of quiescence, usually denotes a malignant transformation. In general, the more rapid the rate of growth, the more malignant the nature of the tumor. Painless tumors are seldom malignant; metastatic carcinoma may be an exception to this rule.

Another valuable aid is the roentgenogram. This will disclose the location of the tumor in the bone as well as its relation to the medullary or cortical portion of the bone.

The portion of long bone involved is a clue to the probable diagnosis. As will be seen by the accompanying illustration (see Fig. 11), each one of the three types most frequently encountered has a predilection for a specific portion of the long bone. For example: endothelioma most frequently involves the diaphyseal area; osteogenic sarcoma, the metaphyseal area; and giant cell tumor, the cancellous bone close to the epiphyseal area. Although exceptions admittedly are found, the fact remains that the majority of these three tumors will be found in the locations as described."

DIFFERENTIAL DIAGNOSIS FROM HISTOLOGIC STANDPOINT

In trying to establish the diagnosis, it has generally been conceded that the microscope is the final arbiter. No doubtful case has been classified by the Bone Sarcoma Registry without a study of tissue sections. Reported

end results that are not supported by pathologic data are regarded as of little value.

While there are many pitfalls associated with histologic diagnosis, the

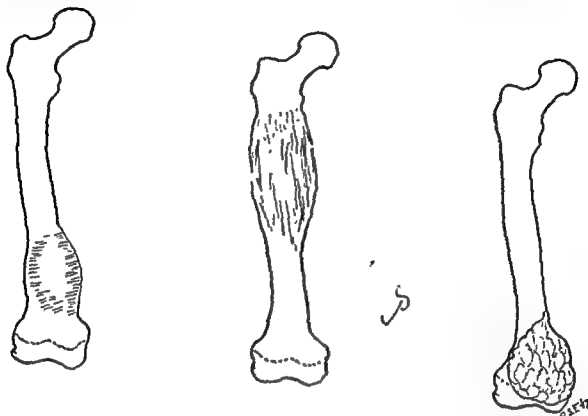


FIG. 11. Sites of predilection in a long bone for the origin of three common primary tumors: *left*, osteogenic sarcoma; *center*, Ewing's sarcoma; *right*, giant cell tumor.

more experienced pathologist will usually, although not invariably, be able to avoid them. Among these may be mentioned the differentiation of frankly benign cartilage tumors from those showing chondrosarcomatous alterations. These alterations may be present in the growing edge of the tumor but not in the necrotic, heavily calcified, or ossified portions. The criteria of malignancy may also be subtle and require examination of many microscopic fields under high magnification. Such cases are not suitable for punch or aspiration biopsy, and to rely on the scanty material thus obtained is to run the risk of error in interpretation. It is not difficult to decide between the benign and the frankly malignant giant cell tumors. However, there may be a gradual, almost insensible, transition from one to the other, and it requires great skill at times to decide whether the case belongs in the aggressive or the truly malignant class. Here the character of the stroma is of the utmost importance and it is this feature, rather than the giant cells, that should be scrutinized most carefully.

Reticulum cell sarcoma resembles diffuse endothelioma so closely that cases have been erroneously classified as examples of the latter by pathologists of wide experience. The same difficulty is found in diagnosing

certain early cases of ossification within muscle (myositis ossificans) which histologically can be readily confused with osteogenic sarcoma. Fibrous dysplasia has been mistaken for medullary fibrosarcoma of bone.

For the reasons given above it is apparent that each case must be studied in its entirety; that is, due weight must be given to the age of the patient and his early history, as well as to the histologic, laboratory, and roentgenographic findings. When these diagnostic aids are at variance with each other the surgeon is justified in proceeding with great caution. He should seek further opinion before accepting a definite diagnosis and particularly before instituting radical surgical measures. Experience has shown that the clinical course may be quite unpredictable where the history, physical findings, roentgenographic and laboratory data, and microscopic picture are in sharp disagreement. In some instances, unwarranted radical surgery has been employed because the surgeon placed undue emphasis on the histologic findings.

It is as important to be able to differentiate between various nonneoplastic lesions of bone and true tumors of bone as it is to be able to recognize which of the tumors of bone is present. The correct diagnosis will enable the surgeon to avoid unnecessary or ill-advised therapy for non-tumorous conditions and to avoid delay in instituting appropriate measures for the true neoplasms. When approaching the problem of diagnosis in a new patient with a bone lesion we have found it convenient and helpful to attempt to reach a solution by a process of exclusion. The first decision to reach is whether or not the condition is a tumor. If the evidence is in favor of it being so then one must decide whether it is benign or malignant, and, if the latter, whether it is primary or metastatic.

On the other hand, if it is considered to be *not* a tumor, it may fall into the classification of inflammatory, posttraumatic, circulatory, endocrine, granulomatous, parasitic, or the miscellaneous group whose etiology remains uncertain (see Table VI).

Table VII, which lists the principal conditions from which the important primary tumors of bone may have to be distinguished, may prove of assistance in the differential diagnosis.

UNCLASSIFIED SARCOMA OF BONE

Histologic confirmation of clinical diagnosis is accepted as the final criterion for classification of bone tumors as well as other neoplasms. It should be pointed out that this is very difficult of accomplishment in a few cases despite adequate material for histologic study. In these cases the pathologist is unable to differentiate on histology alone between several possibilities. Some of these may be classed satisfactorily by correlating the clinical, roentgenographic, and laboratory findings with the histology. There are a few, however, which in spite of thorough exercise of all diagnostic modali-

TABLE VI
METHOD OF DIFFERENTIAL DIAGNOSIS BY EXCLUSION IN A
CASE OF BONE DISEASE*

		TUMOR	
		Chondroblastoma (Jaffe)	
		Chondroma	
		Myxoma	
		Nonosteogenic fibroma (Jaffe)	
		Bone cyst	
		Giant cell tumor, benign	
		Xanthoma	
Benign	Central		
	Central and cortical	{ Angioma of bone Osteoid osteoma Multiple chondrodysplasia (Ollier's disease)	
	Cortical	{ Exostosis Osteoma Osteochondroma	
Malignant	Primary	Monostotic	{ Osteogenic sarcoma Endothelioma (Ewing's sarcoma) Angiosarcoma Reticulum cell sarcoma Liposarcoma
		Polyostotic	{ Plasma cell myeloma Myelocytoma Erythroblastoma Lymphocytoma
	Metastatic	{ Breast Kidney Thyroid Prostate Lung, etc.	
		NOT A TUMOR	
Inflammatory	{	Pyogenic infection (Brodie's abscess)	
		Syphilis	
		Tuberculosis	
Posttraumatic	{	Chronic sclerosing osteitis (Garré)	
		Myositis ossificans	
Parasitic	{	March fracture	
Granulomatous	{	Hydatid disease of bone	
		Letterer-Siwe's disease	
		Hand-Schuller-Christian's disease	
Lipid storage	{	Eosinophilic granuloma	
		Niemann-Pick's disease	
		Gaucher's disease	
Circulatory	{	Calcinosis	
		Aseptic necrosis (caisson disease)	
Endocrine	{	Hyperparathyroidism (Recklinghausen's disease)	
		Acromegaly	
Uncertain etiology	{	Paget's disease (osteitis deformans)	
		Fibrous dysplasia	
		Melorheostosis	
		Osteopetrosis	
		Osteoporosis	
		Spontaneous absorption of bone (phantom clavicle)	

* COLEY, B.L. The diagnosis of neoplasms of bone. *S. Clin. North America* 26:410, 1916

TABLE VII
DIFFERENTIAL DIAGNOSIS

ACTUAL DIAGNOSIS	TO BE DIFFERENTIATED FROM:
OSTEOGENIC SARCOMA	<p><i>Endothelioma</i>, when wide extent of shaft, especially midportion, is involved.</p> <p><i>Giant cell tumor</i>, when purely osteolytic and when area of destruction is confined to epiphyseal area which is the site of giant cell tumors.</p> <p><i>Liposarcoma</i>, although it is extremely infrequent, a roentgenographic distinction may be very difficult.</p> <p><i>Inflammatory bone lesions</i>, sclerosing and lowgrade subacute osteomyelitis.</p> <p><i>Calcifying hematoma</i> (myositis ossificans), unless stereoscopic views are taken showing process to be unconnected with shaft of bone and the cortical line to be intact.</p> <p><i>Metastatic carcinoma</i>. When lesion is apparently solitary it may resemble osteolytic sarcoma.</p> <p><i>Chondroblastoma</i> (Jaffe); <i>Calcifying chondromatous giant cell tumor</i> (Codman). This is a difficult distinction to make and must depend ultimately upon biopsy.</p>
ENDOTHELIOMA	<p><i>Subacute osteomyelitis</i>. This is a most difficult differential diagnosis to make.</p>
GIANT CELL TUMOR	<p><i>Osteogenic sarcoma</i>. These tumors more closely resemble an osteogenic sarcoma but may occasionally suggest a giant cell tumor. They are benign. A biopsy is needed to establish the diagnosis.</p>
CHONDROSARCOMA	<p><i>Chondroma</i>. This may require expert microscopic diagnosis. Small bits of tissue are not sufficient material upon which to base an opinion.</p> <p><i>Chordoma</i>. Rarely seen; may resemble sacral chondrosarcoma. Microscopic appearance of chordoma is distinctive.</p>
PLASMA CELL MYELOMA	<p><i>Metastatic carcinoma</i>. In the absence of evidence of a primary carcinoma this distinction is often impossible without histologic confirmation. Aspiration biopsy of one of the lesions, or sternal marrow puncture, may disclose plasma cells and lead to the correct diagnosis.</p>

ties, must remain as unclassified tumors of bone presenting features of none or several entities. This latter group are very provocative, suggesting as they do that our present concepts of histogenesis may be entirely inadequate.

In considering the various difficulties encountered by the pathologist in interpreting the gross and microscopic histology one must mention inadequate biopsies, tissue from unrepresentative portions of the tumor, biopsies following irradiation or superimposed infection, crushing of the tissue at time of operation or afterward, improper preparation of the tissue, and poor staining.

The cases of bone tumor seen at Memorial Hospital in which the pathologist's report has been equivocal have been reviewed for the purpose of pointing out some of the difficulties of differential diagnosis.

The largest single group comprised those reported simply as "spindle cell sarcoma." Most of these, by correlation with the clinical, radiographic, and laboratory findings, were seen to fit into the class of osteogenic sarcoma, either periosteal or medullary. A few were thought to be soft part sarcomas, e.g., neurogenic or fascial, with secondary bone involvement.

Another fairly large group was listed as "malignant tumor, type undetermined." The majority of these remained in this category.

Problems in the differential diagnosis from the pathologist's standpoint were as follows. (Certain clinical features are listed which warrant careful consideration and may weigh the evidence toward one or the other of the possibilities. It should again be emphasized that full use of all diagnostic measures is frequently necessary in order to determine the type of tumor and that this is desirable before deciding upon the method of treatment.)

Osteogenic Sarcoma (Periosteal type) Versus Neurogenic Sarcoma

1. Gross evidence of association with nerve trunks indicates neurogenic origin.
2. Neurogenic sarcoma tends to involve the bone by extension or pressure from without rather than by destruction originating from within the bone. The radiologist by careful study is frequently able to distinguish these features.
3. Neurogenic sarcoma may be associated with neurofibromatosis in which event stigmata such as café-au-lait pigmentation and other neurofibromata may be found.

Osteogenic Sarcoma Versus Endothelioma of Bone

1. Consideration of the site in the bone and the degree of involvement is of value. Osteogenic sarcoma usually affects the metaphysis whereas endothelioma may involve a wide extent of the diaphysis.

2. The age of the patient may be of value in that endothelioma is unusual in patients over 25 years of age.
3. The presence of bone metastases favors endothelioma as these are common in Ewing's sarcoma and relatively rare in osteogenic sarcoma.
4. If, following biopsy, the tumor proves to be radiosensitive it is probably endothelioma, as osteogenic sarcoma characteristically is radioresistant.

Osteogenic Sarcoma Versus Myositis Ossificans

In deciding between these two conditions the clinical and radiographic features are often more helpful than the microscope. Sections in this type of case should be submitted to a number of pathologists before amputation is decided upon.

1. Myositis ossificans is suggested by the history of trauma followed by sudden development of the growth which rapidly reaches a stationary point and then tends to regress slowly. This condition is more common in the quadriceps group of the thigh and about the elbow.
2. The pain in myositis ossificans diminishes shortly after the acute trauma and is not progressive thereafter. In osteogenic sarcoma the pain is insidious at first but characteristically becomes progressively worse.
3. Stereoscopic roentgenograms are most important aids. In myositis ossificans there is no destruction of the bone, the outline of the cortex being unbroken. All of the new bone production is in the soft tissue.
4. The roentgenographic appearance is confusing only for a short period (ten to thirty days) after the injury. Thereafter simulation of osteogenic sarcoma is not marked.

Endothelioma of Bone Versus Reticulum Cell Sarcoma of Bone

Some pathologists question the concept that reticulum cell sarcoma of bone is distinct from Ewing's sarcoma.

1. Endothelioma has been pointed out to be rare in patients over 25 years of age. Reticulum cell sarcoma on the other hand is not confined to the younger age groups.
2. Roentgenographically endothelioma may involve a wide extent of the diaphysis with an "onion-peel" or "plywood" appearance. Reticulum cell sarcoma produces spotty, spongelike, osteolytic changes with a "cracked ice" appearance, confined to a limited area of the involved bone.

3. Reticulum cell sarcoma shows little tendency to involve other bones, while metastases to bone are common in endothelioma.
4. Both of the tumors are radiosensitive; reticulum cell sarcoma is somewhat more so than endothelioma.
5. The prognosis in reticulum cell sarcoma is far more favorable than in endothelioma.

Endothelioma Versus Lymphosarcoma

The clinical and roentgenographic findings make this differential diagnosis relatively simple. The difficulty is in obtaining microscopic confirmation because of the occasional similarity of the histologic picture.

1. In endothelioma the bone is the primary site of disease; lymph node involvement is not common and occurs late in the course of the disease if at all. In lymphosarcoma lymph node involvement is primary and bone lesions are later manifestations.

Endothelioma Versus Renal Carcinoma

1. Endothelioma is extremely rare in the age group where renal carcinoma has to be considered.
2. Urologic studies may indicate the possibility of a primary renal tumor.

Endothelioma Versus Metastatic Neuroblastoma

This is one of the most difficult differential diagnoses even when all available diagnostic measures are employed. Many cases can be classified only as "endothelioma or metastatic neuroblastoma," with further differentiation impossible. Occasionally the pathologist may be unable even at autopsy to make a positive decision between those two neoplasms.

1. The age of the patients in both groups is similar.
2. Multiple bone lesions are common to both.
3. Radiosensitivity is characteristic of both. Endothelioma may be more sensitive than neuroblastoma but not significantly so.
4. The primary tumor in neuroblastoma very often remains undetermined, particularly in the absence of an autopsy examination.

Carcinoma Versus Adamantinoma

Uncommonly in a long bone lesion the pathologist may report carcinoma and raise the possibility of an adamantinoma. There are less than 20 reported cases of adamantinoma of long bones, all but one (ulna) of which were located in the tibia.

1. Age groups coincide in these two groups of tumors.
2. The presence of primary carcinoma elsewhere would be strong evidence against adamantinoma.

In conclusion it must be conceded that despite the careful correlation of the clinical, roentgenographic, laboratory and histologic features, there will be a small group of neoplasms which must remain in the category of unclassified sarcomas of bone.

CASE REPORTS

Case I

A.T., a 2-month-old Puerto Rican female, was first seen at Memorial Hospital on Dec. 5, 1934, with the history that shortly after a full-term birth spontaneous delivery swelling of the left leg was noted. X-rays taken elsewhere were interpreted as showing possible congenital absence of the distal end of the fibula. The swelling was progressive. She was taken to another hospital where X-rays showed generalized osteoporosis with marked periosteal reduplication and thinning of the cortex of the left tibia. A biopsy was done. Histologic examination was reported as fibrosarcoma. The patient was then referred to Memorial Hospital.

Physical examination revealed in the lower two-thirds of the left leg an irregular, firm swelling, apparently involving the tibia, 7 cm. in length and 16 cm. in its greatest diameter. X-rays of the leg showed considerable deformity of both tibia and fibula, with cystlike areas of absorption in the lower ends of both tibia and fibula. Films of the mediastinum revealed a mass which was considered to be a thymoma.

A review of the microscopic sections was reported as "large spindle cell sarcoma," although Dr. Ewing favored a fat tumor, possibly of medullary bone origin, eroding the cortex. The consensus of opinion was that the tumor originated in the soft parts with secondary pressure on the tibia and fibula.

Irradiation was selected as the method of treatment. From Dec. 8, 1934 through Jan. 23, 1935, 3750 r was delivered to the center of the tumor through 27.8×5.2 cm. ports on the 198-kv. machine with 2 mm Cu at 50 cm. TSD. This was followed by excellent regression. On Apr. 18, it was noted that there was no evidence of tumor. X-rays taken in 1939 showed no evidence of bone involvement of either tibia or fibula, although there was some shortening of the leg. At her last visit, June 10, 1946, there was still no evidence of recurrence.

Ten years after treatment the sections were reviewed and liposarcoma ruled out; this lesion had to be filed as sarcoma, unclassified.

Case II

P.P., a white Italian female of 7 months, was first seen at Memorial Hospital on Oct. 13, 1943, at which time her mother stated that two months previously the child began crying as though in pain. Later the mother noticed swelling of the lower two-thirds of the left thigh, with limitation of motion. X-rays were taken and the child was referred to Memorial Hospital.

Physical examination revealed a tumor on the anterior aspect of the left thigh, oval in shape, measuring 6×4 cm. in its greatest diameter. It extended from just above the knee to the upper third of the thigh. The mass was smooth, hard, fixed to underlying tissues and apparently painless.

X-rays revealed extensive involvement and deformity of the shaft of the left

femur. There was also widening of the mediastinum. The roentgenologist felt that reticulum cell sarcoma or endothelial myeloma should be considered.

Aspiration biopsy was done which was reported as "suggests more a primary bone tumor than a metastatic neuroblastoma and is somewhere in the angioblastic 'Ewing tumor' or reticulum cell sarcoma group." A formal biopsy was done and was reported as "diagnosis lies between Ewing's tumor and metastatic neuroblastoma—favor the latter."

Irradiation was selected as the method of treatment. The left femur was treated through two portals on the 250-kv. machine for an estimated dose of 4210 r to the center of the femur.

When last seen here Feb. 26, 1947, the patient was clinically well except for shortening of the left femur.

5. BLOOD CHEMISTRY IN THE DIAGNOSIS OF DISEASES OF BONE*

HELEN Q. WOODARD, Ph.D.

MUCH CONFUSION HAS EXISTED REGARDING THE SIGNIFICANCE OF CHANGES in the chemistry of the blood and urine of patients with bone tumors. This confusion arises mainly from the fact that most of the chemical changes are nonspecific, several diseases of unrelated etiology being capable of causing the same chemical abnormality. If the mechanism of the chemical changes is understood, a consideration of the laboratory findings will often establish a diagnosis which could not be made by clinical observation alone. The chemical tests whose significance will be considered are those for the total calcium, total protein, inorganic phosphorus, acid and alkaline phosphatase of the serum, and for the calcium and Bence-Jones protein in the urine. These tests are available in the average well-equipped hospital laboratory.

BONE METABOLISM

Before studying the disturbances associated with bone tumors it is necessary to review the conditions which govern the metabolism of normal bone. These are represented diagrammatically in Fig. 12.

Bone consists of a rigid mineral framework imbedded in an organic matrix and enclosing blood vessels and marrow. The principal mineral constituents of bone are calcium phosphate and calcium carbonate in varying proportions[†] (these are shown at the right of the diagram). Of course, all the constituents of bone are derived ultimately from the food; if the latter is inadequate or if absorption from the digestive tract is defective, deficiency disease of bone will result. While bone disease due primarily to protein deficiency has been described, it is not of common occurrence. Bone disease due to deficiency of calcium, phosphorus, or both, is quite

* Part of the material in this chapter appeared in *Archives of Surgery*, vol. 47, pp. 368-383 (Oct., 1943), and is reprinted by the permission of the Editor.

† Superior numbers refer to the Bibliography for this chapter (see p. 72).

common. The principal manifestations are rickets and osteomalacia. These conditions may be caused not only by inadequate diet, but also by faulty absorption due to diarrhea, sprue, or lack of vitamin D.

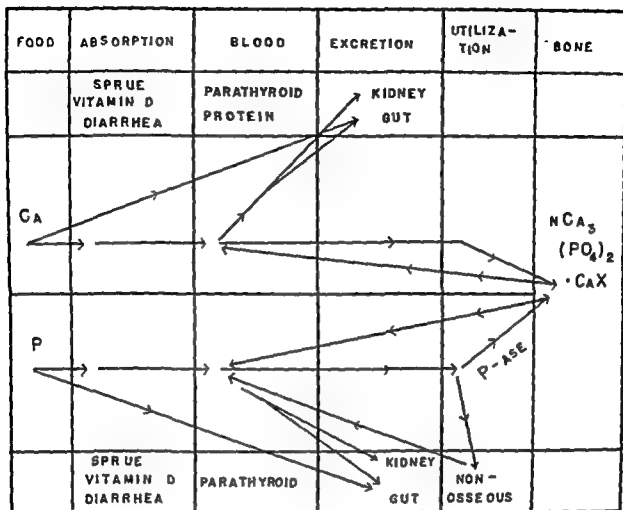


FIG. 12. Factors governing metabolism of normal bone.

After calcium and phosphorus are absorbed from the digestive tract they are transported in the blood stream to the tissues; in the course of normal or pathologic catabolism the tissues ultimately return these elements to the blood for transport to the excretory organs. Calcium is present in the blood in several fractions,⁶ the most important of which are the ionized and the protein-bound.²² The ionized fraction of the serum calcium has an important effect on muscle irritability, and is controlled by the parathyroids. Phosphorus occurs in numerous organic compounds in the blood serum, but the intermediate product in the transformation of these compounds is inorganic phosphate. This, therefore, is the form of phosphorus usually determined in the study of bone disease.

Small amounts of endogenous calcium and phosphorus enter the intestinal tract,²⁴ but most of the calcium and phosphorus in the feces is merely unabsorbed food residue. The principal excretory organ for these elements is the kidney. The rate of calcium excretion by the kidney usually parallels

the blood level rather closely. The renal threshold for calcium is somewhere between 7.5 and 9.0 mg. per 100 cc. of serum; the excretion rises very rapidly when the serum level is above 11.5 mg. per 100 cc.² The renal threshold for inorganic phosphate is lowered by vitamin D and by parathyroid hormone.¹ In severe renal insufficiency phosphate excretion is impaired.

When adequate amounts of calcium and phosphorus reach the bone they are deposited there as complex calcium phosphates. Calcifying cartilage can utilize calcium and phosphorus in inorganic solutions.²⁷ Bones elaborate an enzyme, alkaline phosphatase, which splits inorganic phosphorus compounds to give a local excess of phosphoric acid for deposition as calcium phosphate.²⁶ Many nonosseous tissues contain alkaline phosphatase, but nearly all the alkaline phosphatase in the blood serum originates in the bone.⁴ The enzyme is excreted by the liver, and when liver function is impaired bone phosphatase tends to accumulate in the blood. In subjects with normal livers the alkaline phosphatase of the serum usually parallels rather closely that of the bones.

The alkaline phosphatase of normal adult bone is low while that of growing bone is much higher.^{10, 31, 35} There is a compensatory increase in alkaline phosphates when normal bone growth or repair is prevented owing to inadequate supplies of calcium and phosphorus, as in rickets or hyperparathyroidism.^{5, 7, 8, 11, 19} Alkaline phosphatase is increased when normal new bone is being formed (fractures)^{9, 17, 18, 29, 30} or abnormal new bone is being formed (osteitis deformans, osteogenic sarcoma, or osteoplastic metastatic cancer of bone).^{7, 10, 11, 19, 31, 32, 34} Calcification in nonosseous tissues also may be associated with an increase in alkaline phosphatase.^{23, 29, 34}

While not directly connected with bone metabolism, acid phosphatase is an enzyme whose determination is important in the diagnosis of bone disease. The prostate gland, whether normal, hypertrophied, or cancerous, contains very large amounts of this enzyme, whereas the acid phosphatase of other tissue is by comparison negligible.^{13, 20, 21} The acid phosphatase from the normal prostate or from prostatic cancer, which has not metastasized, does not enter the circulation. When cancer of the prostate metastasizes either to bone or to soft parts excess amounts of acid phosphatase can usually, although not always, be demonstrated in the blood serum.^{12, 14, 15}

CHEMICAL TESTS

In the interpretation of the laboratory findings several factors must be borne in mind. Phosphatase determinations are difficult and tedious, and are reliable only when carried out in a well-equipped laboratory by a skilled technician. Results are reported in arbitrary units which differ according to the method employed; hence, unless the type of unit is specified the

findings are meaningless. For children the normal values for calcium and phosphorus are slightly higher than for adults, and for alkaline phosphatase much higher than the adult normal. Determinations of serum calcium occasionally show gross errors, and in critical cases should be repeated. The final interpretation of the serum calcium depends on the nutritional state of the patient as well as on the possible presence of plasma cell myeloma. An excessive urinary excretion of calcium in a poorly nourished patient might be normal in one who had been ingesting large amounts of calcium.

NORMAL VALUES

Normal* values for the blood and urine constituents commonly studied are as follows:

Serum Alkaline Phosphatase	Adults:	Bodansky Units 1.5-5.0/100 cc. King-Armstrong Units 5.0-17.5/100 cc.
	Children:	from upper adult normal limit to three times this, depending on rate of growth
Serum Acid Phosphatase	Adults:	Bodansky Units 0-1.0/100 cc. King-Armstrong Units 0.6-3.0/100 cc.
	Children:	2.5-4.0 mg./100 cc.
Serum Inorganic Phosphorus	Adults:	4.0-6.0 mg./100 cc. higher in infants
	Children:	10.0-11.5 mg./100 cc.
Total Serum Calcium	Adults:	11.0-12.5 mg./100 cc.
	Children:	6.5-8.0 Gm./100 cc.
Total Serum Protein	Adults:	Urine Calcium: weak to moderate Sulkowitch reaction, depending on diet.
Urine Bence-Jones Protein:		negative.

DIFFERENTIAL DIAGNOSIS

While some types of bone disease may develop at any age, others are much more common in the earlier or in the latter years of life. Therefore it is convenient to consider first the conditions most often seen in children and young adults, and then to group together those more frequently encountered in the middle-aged and elderly. The first group includes benign

* Values outside of the above limits are occasionally seen in apparently normal individuals, if they are persistent they should be viewed with suspicion.

local overgrowths, solitary bone cysts, giant cell tumors, osteogenic sarcoma, endothelioma of bone, and reticulum cell sarcoma of bone; the second group includes metastatic cancer in bone and plasma cell myeloma. In each group the nonneoplastic diseases most likely to be confused with tumors will be discussed.

PRIMARY TUMORS OF BONE

The majority of primary tumors of bone occur in children and young adults, so in interpreting the chemical findings it is necessary to bear in mind that the serum calcium in children is slightly, and the serum inorganic phosphorus definitely, above the adult normal. The serum alkaline phosphatase varies with the rate of growth. A sick child who has ceased growing temporarily may have a serum alkaline phosphatase within the normal limits for an adult, while an adolescent boy may have three times this amount. The alkaline phosphatase usually reaches the adult normal about the time the femoral epiphyses close. In these young patients liver disease is uncommon and seldom needs to be considered in interpreting the phosphatase findings.

CHONDROMA—OSTEOMA

In the numerous abnormalities (chondroma, osteochondroma, osteoma, and exostoses) which are characterized by benign localized overgrowths of bony elements, the abnormal tissue contains about the same amount of alkaline phosphatase as normal bone. There are no changes in the calcium, phosphorus, or phosphatase of the serum. If an elevated alkaline phosphatase is encountered in these conditions, the suspicion is warranted that the local process is undergoing malignant change or that bone disease is present elsewhere in the body.

BONE CYST

The type of solitary bone cyst which occurs in the long bones of children causes no change in the blood chemistry. The normal values for calcium and phosphorus and the absence of significant elevation in the alkaline phosphatase distinguishes these cysts from those caused by hyperparathyroidism.

GIANT CELL TUMOR

The material obtained by curettage of benign giant cell tumors usually contains negligible amounts of alkaline phosphatase and there is no evidence that the bone adjacent to the tumor produces excess of this enzyme except, perhaps, when fracture has occurred. In malignant giant cell tumor tissue there may or may not be considerable amounts of alkaline phosphatase. The serum alkaline phosphatase of patients with benign giant cell tumors is usually in the upper normal range; serum calcium and phosphorus are

normal. In the author's experience, whenever the serum alkaline phosphatase of patients with giant cell tumors has been definitely above normal (6 to 9 Bodansky units), the tumors have shown aggressive tendencies or were frankly malignant. On the other hand the presence of a normal serum alkaline phosphatase does not prove that the tumor is benign.

OSTEOGENIC SARCOMA

Osteogenic sarcoma tissue may contain alkaline phosphatase in amounts ranging from those in normal bone (0.1 to 0.5 Bodansky units per Gm.) to over 100 units per Gm. From 2 to 10 units is the common range. There is no definite correlation between phosphatase activity and histologic type, although the activity of medullary tumors averages somewhat less than that of the cortical type. In general, the greater the new bone formation the more marked the phosphatase activity. There are, however, some extremely malignant tumors which contain abundant phosphatase but which lay down little new bone. If osteogenic sarcoma is treated by external roentgen irradiation, and if the dose to the tumor (not the skin) equals or exceeds 4000 r, the phosphatase-producing mechanism is nearly always completely inactivated. Smaller doses result in irregular or incomplete inactivation. Resumption of tumor growth is accompanied by resumption of phosphatase production.

The alkaline phosphatase in osteogenic sarcoma tissue usually enters the circulation readily and can be measured in the serum. The serum reading may be 10, 20, or even 50 units in excess of the normal for the patient's age. There are, however, some sclerosing osteogenic sarcomas which contain abundant phosphatase but which cause little elevation in the serum readings. Such tumors sometimes have a prognosis better than the average. On the other hand, a very high serum alkaline phosphatase always indicates that the tumor is quite active. If the tumor has failed to lay down new bone the prognosis is especially bad. The calcium and phosphorus in the serum of patients with osteogenic sarcoma are normal.

A review of 110 cases of osteogenic sarcoma shows that the serum alkaline phosphatase was elevated in 61, or 55 per cent, when the patient first presented himself for examination. A few patients whose serum alkaline phosphatase was normal at first later showed an increase in this enzyme so that 64 per cent of all the cases observed had elevated readings at some time.

When a patient with osteogenic sarcoma has a high serum alkaline phosphatase, and the tumor is removed by operation or is inactivated by irradiation, the serum phosphatase falls to normal. Normal levels are reached within two weeks after amputation. If the phosphatase does not drop to normal then residual active disease is present. If the serum alkaline phosphatase of a patient falls to normal and later begins to rise again, metas-

tases are probably developing or an irradiated primary lesion is becoming reactivated. The absence of a rise in phosphatase does not preclude the presence of metastases since some metastatic deposits, though producing

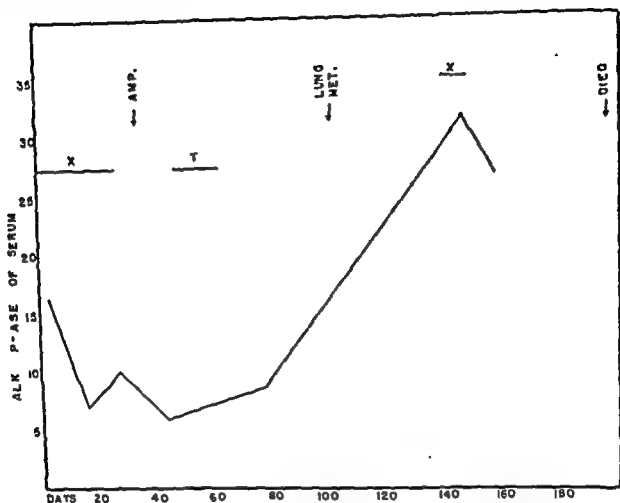


FIG. 13. Changes in the serum phosphatase level in a patient with osteogenic sarcoma. X indicates roentgen therapy; T, treatment by toxins.

phosphatase, do not allow the enzyme to enter the circulation. Thirty-two of our patients in whom the primary tumor was removed surgically and the postoperative serum alkaline phosphatase was normal later developed distant metastases. In 21, or 66 per cent, the appearance of the metastases was associated with a rise in serum alkaline phosphatase. This increase occurred in only half of the cases in whom the metastases were confined to the lungs but in nearly all of those with metastases to bone.

Figure 13 shows the phosphatase changes taking place in the serum of a typical patient with osteogenic sarcoma. The patient, a boy of 13, had an osteogenic sarcoma involving the lower and middle thirds of the shaft of the left femur. His serum alkaline phosphatase was 16.5 Bodansky units per 100 cc., somewhat higher than would be expected in an adolescent boy in rather poor general condition. He received preoperative irradiation, the doses to the upper and lower portions of the tumor being 4100 r and 3300 r

respectively. His serum phosphatase fell promptly to value within the normal range for his age. At amputation, performed five weeks after first observation, the phosphatase-producing mechanism of the tumor was found to have been nearly although not quite inactivated, the readings in various parts of the tumor ranging from 0.34 to 0.82 units/Gm., as compared with 0.20 unit in the normal nonirradiated fibula. The patient received a course of Coley's toxins and appeared to do well for about six weeks. He then developed metastases to the lungs and, shortly afterwards, to the dorsal vertebrae. His serum phosphatase rose to twice the pretreatment level, and irradiation of the vertebral metastases produced little change in the readings. He died less than six months after the date of first observation. At autopsy 4 to 5 units/Gm. of alkaline phosphatase were found in the lung metastases and a somewhat less amount in the irradiated vertebrae. The high phosphatase content of the lung metastases explained the high antemortem serum readings.

ENDOTHELIOMA OF BONE (EWING'S SARCOMA)

As this is a tumor of the endothelial rather than the osseous elements of bone, the tumor itself does not produce significant amounts of alkaline phosphatase. There is usually a certain amount of reaction in the bone surrounding the tumor with production of moderately increased amounts of phosphatase; this may lead to an increase in the alkaline phosphatase of the serum of 1 to 3 units per 100 cc. Such small elevations may be detected with fair certainty in the adult but in the child they are masked by the great variability of the normal values. In an adult with Ewing's sarcoma, the serum alkaline phosphatase may be used in studying the effect of treatment in exactly the same way as it is employed in osteogenic sarcoma; in children, the results of such follow-up studies are too indefinite to warrant subjecting the young patients to venipuncture. Ewing's sarcoma causes no changes in the serum calcium and phosphorus.

RETICULUM CELL SARCOMA OF BONE

In patients with this disease the serum calcium and phosphorus are normal; the serum alkaline phosphatase may or may not be slightly elevated. Thus, the chemical studies are of no help in distinguishing this tumor from endothelioma or inflammatory disease of bone, both of which it often resembles.

RICKETS

A young patient with a bone tumor may also have rickets. The high serum alkaline phosphatase caused by the latter disease should not be confused with that due to osteogenic sarcoma. In the latter, the serum calcium and phosphorus are normal, while in rickets one or both are low.

INFLAMMATORY DISEASE OF BONE

This is often confused with various bone neoplasms and requires separate study. No conspicuous changes in the serum calcium and phosphorus are found in bone inflammations. Except in luetic disease the serum alkaline phosphatase is normal or very slightly elevated. The type of productive osteitis which sometimes resembles periosteal osteogenic sarcoma seldom causes any elevation in serum phosphatase. In such doubtful cases, the higher the phosphatase the more probable is the diagnosis of osteogenic sarcoma, although a normal phosphatase does not exclude osteogenic sarcoma. Osteolytic neoplastic bone disease can not be distinguished from destructive, nonluetic bone infections by means of the blood chemistry. In the author's experience, luetic disease of bone is usually associated with a rather high serum alkaline phosphatase. It is not known whether this is due to excessive production of alkaline phosphatase by the bone or to inadequate excretion of phosphatase by a damaged liver. The combination of an osteolytic bone lesion, a positive serologic test for syphilis, and a serum alkaline phosphatase of 10 to 20 Bodansky units per 100 cc. makes it extremely probable that the lesion is luetic.

METASTATIC CANCER IN BONE

When cancer of soft-part origin metastasizes to bone, the bone may or may not attempt to repair the damage. When little or no attempt at repair is made, little alkaline phosphatase is produced by the bone and the lesion is predominantly destructive. On the other hand, when an attempt at repair is made, abundant alkaline phosphatase is produced and the lesion is osteoplastic. The alkaline phosphatase produced by bones which are the site of carcinoma metastases apparently enters the circulation readily so there is usually a close correlation between the degree of osteoplasia of the lesion, the amount of alkaline phosphatase in extracts of the affected bone, and the amount of alkaline phosphatase in the serum.

The majority of all metastases to bone are osteolytic, those originating in cancers of the breast, thyroid, and kidney being perhaps the most conspicuous. Metastases from cancer of the prostate are almost the only ones which elicit excessive alkaline phosphatase production and new bone formation with great regularity. In our series, in about 80 per cent of patients with metastases to bone originating in cancers of organs other than the prostate, the metastases were predominantly osteolytic. In contrast to this, 75 per cent of the metastases to bone from carcinoma of the prostate were almost wholly osteoplastic, and nearly all the remainder showed some degree of new bone formation. No satisfactory explanation has ever been advanced as to why the bones should differ so much in their response to invasion by different types of cancer. The difference is probably a quanti-

tative rather than a qualitative one since all gradations in degree of new bone formation can be seen in different bones in the same patient; especially in prostatic carcinoma, individual metastatic areas tend to become more osteoplastic with the passage of time.

With the sole exception of metastatic cancer of the prostate, the site of origin of cancer metastatic to bone cannot be determined by chemical means. Despite this, chemical examination of the blood and urine often affords valuable information as to the existence, extent, and activity of bone metastases.

*The typical patient with osteolytic bone metastases has a slightly elevated serum alkaline phosphatase, the readings being perhaps 6 to 7 Bodansky units per 100 cc. The serum calcium and phosphorus tend to be at the upper normal limits or a little above, values in the neighborhood of 12.5 and 4.5 mg. per 100 cc. respectively being common. The urinary calcium excretion is high even on a calcium-poor diet. Even with osteolytic disease the serum alkaline phosphatase may rise as high as 20 units, and calcium and phosphorus values of 16.0 and 5.5 respectively, or even higher, are sometimes seen. Elevations of calcium and phosphorus tend to occur together; the higher the alkaline phosphatase, the less frequent are these elevations. It is probable that the elevation of serum calcium and phosphorus is due to a flooding of the circulation with the end-products of bone destruction. Under ordinary circumstances these are excreted by the kidney without significant alteration in the blood chemistry, but when the rate of osteolysis becomes excessive the kidney can no longer keep pace with it and accumulation in the blood results.

Elevations in serum inorganic phosphorus and serum alkaline phosphatase do not in themselves cause clinical symptoms, although the lesions causing them usually do. Elevations in serum calcium, from whatever cause, may be a serious problem. A serum calcium of 13.0 mg. per 100 cc. or above may cause nausea, lassitude, and mental confusion. Such elevations in serum calcium may occur in patients with metastatic cancer in bone even when they are still in sufficiently good condition to be ambulatory. An erroneous diagnosis of cerebral or gastrointestinal metastases may be made on such cases if the serum calcium is not studied.

*Patients with osteoplastic metastatic cancer commonly show marked elevations in serum alkaline phosphatase, values of 20 to 30 Bodansky units per 100 cc. being common, and values in excess of 100 units being seen occasionally. In these patients the calcium and phosphorus of the serum are not elevated, and, indeed, the calcium averages somewhat below normal. The urinary calcium excretion is within normal limits. In these metastases the large amounts of alkaline phosphatase produced by the damaged bone are sufficient to protect it from disintegration. The process is not capable of preserving normal bone structure, but it is able to preserve the

bone constituents. There is, therefore, no flooding of the circulation with breakdown products, and the serum calcium and phosphorus do not rise.

In actual practice, patients are often encountered whose blood chemical findings present a picture intermediate between those of the two groups described, and some cases of known metastatic cancer to bone show no abnormalities in blood chemistry. A review of the blood chemistry of 250 of our cases with known bone metastases shows that in about 75 per cent an elevation of either calcium, phosphorus, or alkaline phosphatase was present. Therefore, although normal blood chemical findings give no assurance that bone metastases are absent, they make the presence of such metastases somewhat improbable. An elevated serum alkaline phosphatase, on the other hand, nearly always indicates that either bone or liver disease is present. As the alkaline phosphatase will not distinguish between bone disturbances and metastatic or other disease of the liver, it is necessary, before accepting an elevated serum alkaline phosphatase as definite proof of bone metastases, to be certain that there are no signs of liver disturbance.

As explained above, the prostate gland, whether normal, hypertrophied, or cancerous, contains large amounts of acid phosphatase. So far as is known at present, this enters the circulation only when a cancerous prostate has ruptured its capsule. An elevation of serum acid phosphatase is considered pathognomonic of metastasizing carcinoma of the prostate, and the elevation may occur whether the metastases are to soft parts or to bone. The presence of a normal serum acid phosphatase does not exclude a diagnosis of metastasizing prostatic cancer. In our series of 61 cases of prostatic cancer with known bone metastases, 69 per cent had elevations in the serum acid phosphatase when first seen; of 37 cases of prostatic cancer with evidence of soft-part extension, but without known bone metastases, 41 per cent had elevations in serum acid phosphatase. In the majority of cases with initial normal readings, the serum acid phosphatase rose later in the course of the disease. In a few patients, either because the tumor does not produce large quantities of acid phosphatase or because the enzyme does not enter the circulation, the serum acid phosphatase never rises much above the normal limits. We have seen patients in a terminal stage of metastatic prostatic cancer whose serum acid phosphatase was only 2 to 3 Bodansky units per 100 cc., and others with readings of 100 units or, as in one case, 300 units. For this reason, the serum acid phosphatase at any one time does not give a reliable indication of the activity of the disease; however, changes in the serum acid phosphatase in any one patient may be regarded as a sensitive indication of his clinical progress. In particular, a prompt drop in the serum acid phosphatase after the institution of endocrine therapy shows that a favorable clinical response may be anticipated; failure of the serum acid phosphatase to drop within one to two weeks indicates that the patient is probably refractory to this type of treatment;

and a rise in the acid phosphatase of the serum of a patient who has previously shown a satisfactory drop is indicative of a clinical relapse, to take place within one or two months.

The great majority of metastases to bone from carcinoma of the prostate show a significant degree of new bone formation. These patients exhibit with great regularity an elevation in serum alkaline phosphatase; in this respect they do not differ from patients with osteoplastic metastases from cancers originating in other organs. It must be emphasized that in the serum of patients with carcinoma of the prostate metastatic to bone the acid phosphatase is produced by the cancer in the bone or in other regions, while the alkaline phosphatase is produced by the bone around the cancer. The two enzymes may, and frequently do, vary independently. Patients with bone metastases from carcinoma of the prostate, who are receiving endocrine therapy, often show a rise in the serum alkaline phosphatase during the first one or two months after the beginning of treatment, followed later by a drop to or towards normal levels. The presence or absence of this rise is not related to clinical response. The cause is obscure and cannot be discussed in detail here.

LYMPHOMATOID DISEASES

When the bones are involved by diseases of the lymphoma group the same changes in blood chemistry may be produced as those which are seen in patients with carcinoma metastatic to bone. However, in the lymphomatoid diseases liver function is often severely impaired, and this may result in retention of alkaline phosphatase in the blood. Especially in the leukemias, where the bone lesions are usually osteolytic, changes in the serum alkaline phosphatase due to bone disease are usually obscured by liver disturbances. In Hodgkin's disease the relation between elevations in serum alkaline phosphatase and the presence of bone involvement is a little closer, but even here great caution should be used in interpreting the alkaline phosphatase findings.³³

PLASMA CELL MYELOMA

This disease, like endothelioma of bone, is a disease in bone but not of bone. Because it occurs in the later age groups and results in bone destruction, it is often difficult to distinguish from metastatic disease. When active and uncomplicated it resembles osteolytic metastatic disease in causing slight elevations in serum alkaline phosphatase, serum phosphorus, and serum calcium. The reason for these changes is the same in both conditions. The serum alkaline phosphatase is elevated in only about 25 per cent of the cases of plasma cell myeloma. The serum acid phosphatase is normal. The distinguishing chemical change in plasma cell myeloma is in the protein constituents of blood and urine. It has been known for many

years that about 60 per cent of patients with plasma cell myeloma excrete Bence-Jones protein in the urine at some time during their illness. It has been shown²¹ that in plasma cell myeloma there may be one or several of a group of abnormal constituents in the globulin fraction of the serum. These may or may not result in a marked increase in the total serum protein. In the average hospital laboratory it is not possible to make protein fractionations such as these, but it is possible and easy to determine total serum protein and urinary Bence-Jones protein. If a patient with osteolytic bone disease has a positive test for Bence-Jones protein in the urine, or a total serum protein of 8.5 Gm. per 100 cc., or both, it is reasonably certain that he has plasma cell myeloma. Negative findings do not exclude this diagnosis. Similar changes are sometimes observed in liver disease, leukemia, and lymphogranuloma inguinale, but these can usually be distinguished clinically from plasma cell myeloma. Severe kidney impairment is common in plasma cell myeloma, and the very high serum inorganic phosphorus sometimes found may be due to retention of phosphorus by the damaged kidney rather than to excessive osteolysis.

There are two types of nonneoplastic bone disturbance which occur in elderly people, especially women, which may readily be confused with neoplastic disease of bone. They are osteomalacia and senile osteoporosis. They are characterized by demineralization, which occurs in the entire skeleton but which is most conspicuous in the spine, where it leads to collapse of vertebrae, pain, disability, and deformity.

OSTEOMALACIA

This condition in the adult is the analogue of rickets in the child. It is caused by insufficient intake or faulty absorption of calcium, phosphorus, protein, or all three. Patients with this disturbance, although they may be fat, always appear ill-nourished. They are notoriously unreliable in their accounts of what they eat but when a satisfactory history can be obtained it will show either long-continued poor diet or chronic indigestion. In these cases, the serum calcium, phosphorus, protein, or all three may be low according to the nature of the deficiency. The changes are not very marked, typical values being: calcium 9.0 to 9.5 mg. per 100 cc.; phosphorus 2.2 to 2.5 mg. per 100 cc.; protein 5.8 to 6.2 mg. per 100 cc. There is apt to be compensatory hyperparathyroidism so that in cases in which the main deficiency is in phosphorus and the calcium intake has been adequate, the serum calcium may be increased to 12.0 or 12.5 mg. per 100 cc. instead of being decreased. In osteomalacia the reparative mechanism of the bones is normal; hence the alkaline phosphatase in the serum is elevated.

Unfortunately for the problem of *differential diagnosis*, patients with metastatic bone disease are frequently ill-nourished, and prolonged observation is often necessary in order to disentangle the multiplicity of dis-

orders. In addition, patients with cancers of the gastrointestinal tract, but without bone metastases, often have bone changes due to faulty absorption of food. In doubtful cases it is sometimes helpful to give large doses of calcium, phosphorus and vitamin D, and to follow the Sulkowitch reaction of the urine. If the primary disturbance is calcium deficiency, the excess calcium intake will be stored and the Sulkowitch reaction will not rise. In metastatic cancer to bone the excess calcium cannot be used to repair the bone defects; it will overflow in the urine.

SENILE OSTEOPOROSIS

This disease, described by Albright,³ is due to a defect in the regenerative mechanism of bone which, in turn, is probably caused by the endocrine imbalance of later life. Because of the defect, the normal wear and tear on the bones cannot be repaired and severe demineralization results. The disease is much more common in women than in men, and usually has an insidious onset dating from the menopause. All blood chemical findings are normal and the Sulkowitch reaction corresponds to the calcium intake. The absence of an elevation in the serum alkaline phosphatase serves to distinguish this condition from osteomalacia and in many cases from metastatic cancer in bone. In patients with senile osteoporosis the defective bone cannot utilize the additional building materials made available by large doses of calcium, phosphorus, and vitamin D, and the excess calcium spills promptly in the urine where it can be detected by a rise in the Sulkowitch reaction.

HYPERPARATHYROIDISM

This condition, known variously as *von Recklinghausen's disease* and *osteitis fibrosa cystica generalisata*, is due to the increase in serum calcium and the lowering of the renal threshold for phosphorus, which are brought about by excess parathyroid hormone. The result is a loss of large amounts of calcium and phosphorus in the urine with corresponding depletion of the stores in the bones. In the typical case there are multiple fibrocystic bone changes, nephrolithiasis, and symptoms of hypercalcemia. The serum calcium may be anywhere from the upper normal limit to 18 or more mg. per 100 cc.; the serum inorganic phosphorus may be from the lower normal limits down to 1.0 mg. per 100 cc. The urine Sulkowitch reaction parallels the serum calcium and may be very high. The serum alkaline phosphatase is elevated, the degree of elevation varying with the extent of bone damage and sometimes reaching 50 Bodansky units per 100 cc. The low serum phosphorus will distinguish hyperparathyroidism from osteolytic metastatic cancer in bone. Inasmuch as borderline changes in serum calcium and phosphorus may occur from emotional or other temporary causes, the de-

terminations should always be made at least twice on blood samples drawn on different days.

While the typical case of hyperparathyroidism shows a high serum calcium, low serum inorganic phosphorus, high serum alkaline phosphatase, and high Sulkowitch reaction, the disease exhibits many confusing variations. Thus, a recent acute case on a high calcium diet may have a dangerous hypercalcemia and staghorn calculi in the kidneys but only mild demineralization of bone, the high calcium diet having protected the bone from destruction. On the other hand, a mild case of many years' standing on a low calcium diet may have such extreme demineralization that the serum calcium can no longer rise and may even be below normal. Another complication may be found in cases where kidney stones have been present long enough to cause severe renal insufficiency. Here the damaged kidney can no longer maintain a low threshold for phosphorus, and the serum phosphorus instead of being below normal may be high. In these patients, other signs of kidney disease are readily discovered. Thus while in typical cases hyperparathyroidism may easily be distinguished by the blood chemistry from metastatic cancer in bone, this disease is often accompanied by secondary changes which must be taken into account before a differential diagnosis can be made.

It is well known that immediately after the removal of a parathyroid tumor which has been causing hyperparathyroidism, the patient often goes into an acute hypoparathyroid crisis. This is characterized by a rise in serum inorganic phosphorus and a drop in serum calcium, the latter condition leading to tetany. Since a satisfactory serum calcium determination cannot be made in less than from six to eight hours after the blood is drawn, there may be dangerous delay in the institution of therapy. It is well, therefore, to remember that a sudden rise in serum inorganic phosphorus is as reliable an indication of hypoparathyroidism as is a sudden drop in serum calcium, and that serum phosphorus determinations can be made in less than one hour.

OSTEITIS DEFORMANS (PAGET'S DISEASE OF BONE)

The roentgenographic picture in this condition often resembles that of carcinoma of the prostate metastatic to bone. In osteitis deformans, the serum calcium, phosphorus, and acid phosphatase are normal; the alkaline phosphatase is greatly elevated, sometimes reaching 200 Bodansky units per 100 cc. although values of from 20 to 40 units are more common. If the acid and the alkaline phosphatase of the serum are above normal, the patient has metastasizing carcinoma of the prostate. He may also have osteitis deformans, but this is not likely. If there is a very high serum alkaline phosphatase and a normal serum acid phosphatase, he probably has osteitis deformans, but this is not certain since some patients with

metastasizing carcinoma of the prostate have no elevation in serum acid phosphatase. A very high serum alkaline phosphatase in a female will not in itself establish a diagnosis of osteitis deformans since any condition in which large amounts of new bone are being formed will raise the serum alkaline phosphatase. Nevertheless, the serum alkaline phosphatase in osteitis deformans is often so high that there can be little doubt of the diagnosis, especially in a patient in good general condition without severe symptoms.

Many observers have found that the serum alkaline phosphatase of patients with osteitis deformans shows little variation over a period of years. We have confirmed this observation in general but have found occasional exceptions. A few patients whose serum alkaline phosphatase had been constant for several years showed a sudden rise to double the usual value. Simultaneously there was an increase in symptoms; one patient developed osteogenic sarcoma. The average osteogenic sarcoma does not contain more alkaline phosphatase per gram of tissue than does the bone of osteitis deformans. Hence, the rise in serum phosphatase in this case was probably not due to the presence of the sarcoma, but was an indication of an increase in bone activity which in turn led to malignant change. We have also found that just as an acute illness may stop normal bone growth in a child so systemic disease may reduce bone activity in osteitis deformans, with accompanying drop in serum alkaline phosphatase in both cases.

SUMMARY

The accompanying table summarizes the chemical findings in typical cases of various neoplastic diseases of bone, and in the nonneoplastic diseases most likely to be confused with them. The first eight entries show conditions most commonly found in children and young adults; the remainder show those more frequently found in older patients. Where a space is left blank, detailed studies are lacking, but abnormal values have not been reported.

In the primary bone tumors there is no disturbance in the calcium and phosphorus of the blood. The alkaline phosphatase of the serum is elevated when the tumor is forming new bone rapidly. The increase does not depend on whether or not the tumor is malignant, but merely on the rate of bone formation. Hence an increase in serum alkaline phosphatase is not pathognomonic of any one type of bone tumor. Such an increase is, however, so much more frequent and striking in osteogenic sarcoma than in other primary bone tumors that its presence may serve to clinch a diagnosis in doubtful cases. The degree of elevation of the serum alkaline phosphatase is always a good indication of the activity of a bone tumor, even though it gives no unequivocal indication of the nature of the tumor. Youthful patients in whom bone tumors are common may also have rickets, but the

CHEMICAL DETERMINATIONS IN TUMORS AND IN OTHER LESIONS OF THE SKELETAL SYSTEM

DISEASE	SERUM ACID P-ASE	SERUM ALK. P-ASE	SERUM INORGANIC PHOSPHORUS	TOTAL SERUM CALCIUM	URINE SULKOWITCH	URINE B-J PROTEIN	TOTAL SERUM PROTEIN
Chondroma		Normal	Normal	Normal			
Osteochondroma							
Osteoma							
Exostoses							
Solitary bone cyst		Normal	Normal	Normal			
Giant cell tumor	Normal	Normal or sl. raised	Normal	Normal			
Osteogenic sarcoma	Normal	Usually high	Normal	Normal			
Endothelioma of bone		Normal or sl. raised	Normal	Normal			
Reticulum cell sarcoma of bone		Normal or sl. raised	Normal	Normal			
Rickets		High	Normal or low	Normal or low			
Inflammatory disease of bone		Usually normal	Normal	Normal			
Osteolytic metastatic disease	Normal	Normal or mod- erately raised	Normal or high	Normal or high		Negative	Normal
Osteoplastic metastases not from prostate	Normal	High	Normal	Normal	Normal	Negative	Normal
Carcinoma prostate metastatic to bone	High in 70% of cases	High	Normal	Normal	Normal	Negative	Normal
Plasma cell myeloma	Normal	Normal or sl. raised	Normal or high	Normal or high		Positive in 60% of cases	Normal to very high
Osteomalacia	Normal	Moderately raised	Normal or low	Usually low	Usually low		Normal or low
Senile osteoporosis		Normal	Normal	Normal	Normal		Normal
Hyperparathyroidism		High	Low	High	High		
Osteitis deformans	Normal	High	Normal	Normal	Normal		Normal

NEOPLASMS OF BONE

disturbances in serum calcium and phosphorus which occur in this disease distinguish it from other conditions in which the serum alkaline phosphatase is also elevated. Inflammatory disease of bone cannot be distinguished chemically from tumors of bone.

In cancer metastatic to bone, the alkaline phosphatase of the serum is elevated if new bone is being formed. If new bone is not being formed the serum alkaline phosphatase is not elevated, but if destruction of bone is proceeding very rapidly the serum calcium and phosphorus frequently are elevated. These changes depend entirely on the type of reaction in the bone, and not at all on the type of tumor which has metastasized to bone. If carcinoma of the prostate metastasizes to bone or to soft parts, the acid phosphatase of the serum is usually elevated. This change is specific for metastasizing prostatic carcinoma.

In plasma cell myeloma the changes in the calcium, phosphorus, and alkaline phosphatase of the serum are similar to those seen in osteolytic metastases from carcinoma. In many cases of plasma cell myeloma there are distinctive changes in the proteins of blood and urine.

Nutritional osteomalacia and hyperparathyroidism, which cause bone changes somewhat resembling those of metastatic cancer of bone, can often be distinguished by the changes which they cause in the calcium and phosphorus of the serum.

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SECTION TWO

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INTRODUCTION TO SECTION TWO

WHILE BY THE TERM BENIGN IS MEANT THOSE LESIONS WHICH DO NOT tend to metastasize nor to recur if completely removed, nevertheless many of the types listed as benign have serious potentialities. For example, the majority of adamantinomas which are not completely removed will continue to recur and to extend until they may end fatally (see Figs. 253-255, pp. 436-438). Central chondroma has a marked tendency to undergo a gradual transition to chondrosarcoma. An appreciable percentage of giant cell tumors will become sarcomatous. Fibrous dysplasia has been reported as being the site of subsequent osteogenic sarcoma.

It is therefore important not only to recognize the existence of these innocent neoplasms but to decide which ones are to be treated and under what conditions, in order to avoid the serious sequelae which may later become manifest.

On the whole, benign bone tumors are relatively more common than is generally appreciated. Many are never suspected and a considerable number are identified only as a result of roentgenographic study made for some other reason, usually after an injury. While statistics based on hospital admissions or outpatient clinics are therefore an unreliable index of the frequency of these lesions it is the author's belief that they occur more often than do primary malignant tumors of bone.

There are certain clinical attributes which, being common to most benign tumors, may be briefly mentioned.

SYMPTOMS

Most benign tumors of bone are of slow growth, tend to expand but not to invade normal bone, and cause pain only infrequently and to a much milder degree than do the malignant varieties. Often a swelling is the first symptom noted by the patient, and he may postpone seeking medical attention for years. He usually maintains that the size of the swelling has remained stationary or that it has increased by insensible gradations. It may concern him chiefly by its prominence or by its interference with some particular function or activity. When pain is felt it seldom increases in

severity as does the usual malignant process in bone. At times a deform is noted either by the patient or by some member of his family.

ROENTGENOGRAPHIC FEATURES

While it must be conceded that at times it is exceedingly difficult determine from the roentgenogram alone whether a tumor of bone benign or malignant, there are certain features which are strongly suggestive of a benign process and in the majority of cases one can be fairly certain of the diagnosis.

In tumors which arise within the bone one is able to detect a circumscribed appearance in the involved area. The edges of the lesion have sharp border and irregular bone destruction is usually absent. Expansion unaccompanied by such destruction is commonly encountered and is particularly apparent in bone cyst, giant cell tumor, fibrous dysplasia, and central chondroma. The pattern in most osteochondromas is so characteristic that it is almost pathognomonic. Seldom is the entire cortex of bone absorbed save in advanced stages of giant cell tumor of aggressive borderline nature. The periosteal covering of the affected area remains intact, broken and serves to confine the process.

In some varieties of benign tumor of bone, notably the osteochondroma the lesion may distort the unaffected paired bone, e.g., the ulna or fibula when the radius or tibia is involved. This appearance is the result of mechanical pressure and is similar to changes wrought by weight-bearing muscular pull in cases of paralysis which is induced by unopposed muscle groups, and other conditions. Brailsford has recently called attention to the fundamental plasticity of bone and credits John Hunter with a familiarity with it more than a century ago. Since the distortion is produced by prolonged pressure its presence is indicative of a slowly progressive process and therefore one that is nearly always benign (see Fig. 39, p. 105).

The treatment of benign tumors of bone has never been standardized. The tendency has been to leave them alone unless they were causing symptoms. We believe that a more aggressive attitude is desirable and that surgical removal were more widely practiced there would be a saving of many lives now lost because of malignant transformation. There is legitimate reluctance to subjecting a symptomless patient to an extensive operation on a benign tumor situated in an inaccessible bone; but there seems no absolute contraindication to removing one in an accessible location.

Roentgen therapy has seemed an illogical method of dealing with benign bone tumors which are for the most part no more radiosensitive than normal bone. The giant cell tumor, however, has in the past been treated in many institutions by roentgen-rays. The same may be said, to a lesser degree, for bone cyst. Further details will be given in the sections dealing with these diseases.

6. OSTEOMA

CLASSIFICATION AND ETIOLOGY

THE TERM "OSTEOMA" SHOULD BE RESERVED, STRICTLY SPEAKING, FOR THE benign neoplasms composed of osseous tissues. Such tumors are actually rather uncommon. They may take several forms, e.g., the dense

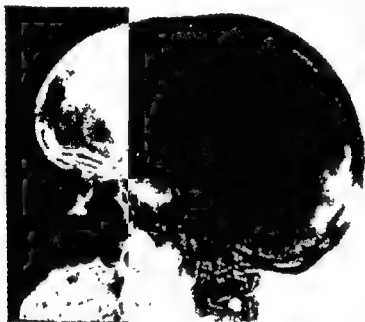


FIG. 14. Osteoma of sella turcica. Although benign, this tumor caused the death of the patient by pressure erosion of the circle of Willis.

ivorylike osteoma eburneum, the hard, dense osteoma durum, and the softer cancellous structures with numerous marrow cavities, osteoma spongiosum. Classified according to their location, they are either central, endosteal, cortical, or periosteal. Dental cases originating in dentine tissue form a distinct group termed odontomas. Ewing has stated that "it has never been possible to exactly define the limits of osteoma."

Since osteomas arise from osteoblasts and since these cells are found in greatest numbers in the area adjacent to periosteum or endosteum, these locations are the usual source of osteoma. They rarely arise from scattered osteoblasts found elsewhere in bone. Some undoubtedly originate on a hyaline cartilage basis. Volkmann considered that those exostoses which

arise from cartilage are true tumors whereas others are not. Borst removes from the tumor field all self-limiting processes or those obviously associated with injury or infection; in consequence he has little to say regarding true osteoma.



FIG. 15. Huge osteoma of dense, almost marble-like composition. Histologically benign. X-ray appearance closely resembles sclerosing osteogenic sarcoma.

CLINICAL FEATURES

Rate of growth is ordinarily extremely slow, little discomfort is caused, and intrinsic pain is negligible. Where symptoms are produced they are due to pressure on nerves, blood vessels, or overlying soft parts. Where the tumor occupies unusual locations there may be serious consequences; for example, a case was seen where an osteoma of the sella turcica caused necrosis from pressure on a cerebral vessel with fatal intracranial hemorrhage (see Fig. 14).

Long bone osteomas are often seen in a form which is termed exostosis. These vary greatly in size and shape, being nodular, flat, pedunculated, pointed, etc. (see Fig. 15). They are circumscribed and elevated above the normal contour of the bone in contrast with enostoses which lie within the bone. Most of these have a cartilaginous component, usually in the form of a cap overlying the projecting portion. This fact actually places

them in the category of osteochondroma. Exostoses should be distinguished from the various simple hyperplastic overgrowths of bone such as are seen at the insertion of certain tendons, in organizing hematomas, in necrotic tissue, and in the muscles of the adductor and gluteal groups in cowhands and cavalrymen. Such a distinction must be based on clinical and gross features rather than on histologic differences. The term osteophyte is used to define an inflammatory cortical or supracortical deposit of bone from the periosteum.

Osteoma of the cranial bones and bones of the face and jaws are not unusual, with the ethmoids, sphenoids, and orbital bones predominating (see Fig. 16). In the long bones, the femur, scapula, pelvis, and humerus are usual sites. In such locations there is often an overlying bursal covering. These bursae may be directly connected with the synovial membrane of the nearby joint or entirely adventitious.

ROENTGENOGRAPHIC APPEARANCE

There is little difficulty in interpreting roentgenograms of osteoma, the absence of bone destruction, the regular smooth outline, and the failure to



FIG. 16. Osteoma of right ethmoid bone.

produce soft part tumor are criteria of benign neoplasms. Films reveal the absence of irregular calcific deposits which are features of osteochondroma.

TREATMENT

Because many of these tumors cause negligible symptoms or are entirely innocuous, and since there is little, if any, likelihood of malignant metaplasia, they frequently require no treatment. If they cause pain or circulatory disturbances because of pressure they should be resected if accessible. This is in contrast to osteochondroma, which requires a definite removal because of the possibility of metaplasia and therefore should be removed.

7. OSTEOID OSTEOMA

CLASSIFICATION AND ETIOLOGY

IN 1935, THE ENTITY KNOWN AS OSTEOID OSTEOMA WAS FIRST DESCRIBED BY Jaffe. In the following decade he has encountered 62 proved cases. The condition is now rather widely recognized both here and abroad. Jaffe defines it as "a small, oval or roundish, niduslike benign neoplasm of bone. When well advanced in its evolution, it consists, in varying proportions, of osteoid, trabeculae of newly formed osseous tissue, and a substratum of highly vascularized osteogenic connective tissue. The lesion usually does not exceed a centimeter in its greatest dimension, and in a given affected bone may lie within the spongiosa (perhaps at or near an articular surface), or against the inner surface of the bone cortex, or even actually within the cortex. Though the niduslike focus is the osteoid osteoma *per se*, the total abnormal area in the affected bone may be very large since there may be a perifocal zone of bone thickening or sclerosis extending for a considerable distance beyond the nidus."¹

It has a predilection for the male sex in the proportion of two to one, and for adolescents with the period from 11 to 26 years accounting for three-fourths of the cases. It affects the lower limbs more often than the upper. It appears in the vertebral column and pelvis. However, the femur and tibia account for about half of all cases. It is an uncommon lesion but is not rare. Presumably a certain number of cases are overlooked or are given some other diagnosis, e.g., sclerosing osteitis (Garré).

There are two principal theories regarding the nature of osteoid osteoma. Jaffe originally maintained, and has since reaffirmed the opinion, that the process is a true primary benign tumor of bone. He concedes that those who differ with him have some justification for their belief that it is not a neoplasm but a response to a nonsuppurative bone infection. Most authorities seem inclined to accept the views expressed by Jaffe, although they are opposed by Brailsford in England and by Ghormley and his associates in America.

¹ JAFFE, H. L. "Osteoid-osteoma": Benign osteoblastic tumor composed of osteoid and atypical bone. *Arch. Surg.* 31:709, 1935.

In support of Jaffe's contention is the fact that almost without exception cultures taken from these lesions at operation have failed to establish causative organism and have remained sterile. On the other hand the



FIG. 17. Osteoid osteoma. Note that the central radiolucent area (nidus) is only apparent on one of the views. This again emphasizes the importance of making exposures in several planes.

appearance of the lesion on roentgenograms is certainly suggestive of a subcortical bone abscess which has produced a minimal area of bone destruction but which has evoked a pronounced sclerosing response on the part of the bone surrounding it.

If in the future it is found to be the result of an infection the author believes that the offending organism will prove to be an uncommon cause of bone infection and may even be a virus disease. Such a theory is admittedly pure speculation and for the present it is safe to accept Jaffe's theory since the treatment based thereon has given such consistently satisfactory results.

CLINICAL FEATURES

Pain is the primary complaint and prior to seeking surgical relief the duration may have been a matter of many months or even years, the average period being from six to twenty-four months. The pain is mild and inconstant at first but increases in degree and persistence until it may keep

the patient awake at night. Swelling may or may not be apparent depending on the amount of overlying soft parts. Disability and limp may be complained of in lower extremity cases. Fever is consistently lacking. Tenderness is localized specifically to a point in the area where pain is felt. Heat and erythema are conspicuously absent.

Only 30 per cent of Jaffe's cases gave a history relating the onset of symptoms to a local injury. Trauma has not been shown to be an etiologic factor.

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ROENTGENOGRAPHIC FINDINGS

The X-ray films give the most valuable information on which to make a diagnosis, for this picture is characteristic (see Figs. 17 and 18). There is a dense, sclerotic, relatively radiopaque zone about a small oval or round area of radiolucency. This latter area is termed the nidus. The extent of the sclerotic zone varies but may be visible for three or four centimeters. The nidus may appear in the spongiosa or in the cortex; in the latter cases, half or more of the circumference of the shaft may be affected.

In early cases the evolution of these roentgenographic features may not be sufficient to permit of a diagnosis. Moreover, when the cortex of a long bone is involved and much sclerosis is present, an ordinary routine film may fail to disclose the nidus, which is clearly visible if spot films are made with greater exposure and in several planes.

One should remember, too, that early in the course of symptoms the roentgenographic examination may be negative but subsequent films will reveal the true nature of the process. Reexamination a few months later should therefore be insisted upon.



FIG 18 Osteoid osteoma of upper third of tibia in a 2-year-old child. Diagnosis confirmed by operation. The nidus is not clearly shown in this view.

DIFFERENTIAL DIAGNOSIS

Localized, low-grade bone infection of the sclerosing type (Garré) is sometimes very difficult to distinguish from osteoid osteoma. Brown and Ghormley in this country and Brailsford in England even question the concept of osteoid osteoma and consider it to be a cortical bone abscess, or a chronic subperiosteal bone abscess. We have in the past seen 2 cases in which the roentgenographic features suggested the possibility of the lesion being an early osteogenic sarcoma.

TREATMENT AND PROGNOSIS

Surgical removal of the lesion is followed by a lasting cure of the symptoms. Block removal is best for it gives the pathologist an opportunity to make a microscopic diagnosis. However, a thorough curettage will be curative if it removes the entire nidus. The ultimate fate of untreated cases cannot be predicted although Jaffe believes it is conceivable that after years the lesions "may undergo spontaneous clinical arrest or even anatomic involution."

The author saw a case in which an osteogenic sarcoma developed nine years after treatment with roentgen-rays. Little is known of the possible effect of radiation therapy upon osteoid osteoma. In general, however, surgical removal yields satisfactory results and until some more specific method of treatment is discovered it appears to be the method of choice.

Provided the removal of the nidus was complete most of the reported cases have yielded excellent results. The relief of pain following this procedure is sometimes most dramatic, the patient soon after recovering from the anesthesia volunteering the information that the long-standing pain has disappeared completely.

8. NONOSTEOGENIC FIBROMA OF BONE

A DISTINCT CLINICAL ENTITY HAS BEEN DESCRIBED BY JAFFE WHICH IS characterized by a single or several closely adjacent areas of rarefaction, occurring usually in the upper or lower third of an extremity of a long

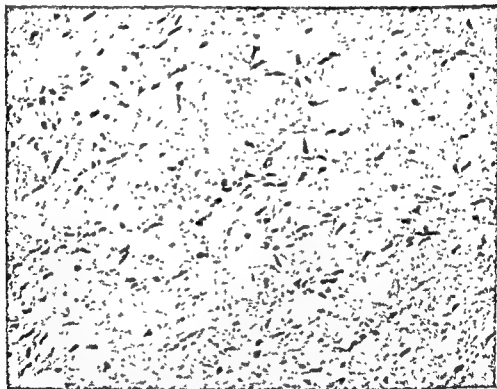


FIG 19. Nonosteogenic fibroma of bone. Tumor relatively acellular. No bone production in any portion of the tumor.

bone and more often involving the lower extremity than the upper. The affected area is sometimes eccentrically placed; at other times it extends completely across the diameter of the bone. The larger the bone the less often the area extends across the shaft, and when it does it generally causes a bulging of the shaft. The condition is benign, arising from connective tissue of the marrow which does not undergo osseous metaplasia.

Symptoms are usually mild and of short duration, although probably

the process is of long standing and attention to it may have been attracted as a result of some irrelevant trauma (traumatic determinism). In cases without history of injury, pain and swelling are the chief complaints. No



FIG. 20. Nonosteogenic fibroma of bone. This was regarded at first by the pathologist as a fibrosarcoma of bone. Undoubtedly in the past this benign neoplasm has been termed malignant and such cases would then have been recorded as "cures."

doubt routine films would disclose a number of entirely unsuspected cases; in fact, some were thus discovered in Army hospitals.

Jaffe describes the gross tissue as yellowish or brownish in color, and microscopically it is seen as a mass of whorled bundles of spindle-shaped connective tissue cells. Multinuclear giant cells and, more often, foam cells are seen (see Fig. 19).

There are several conditions which on roentgenographic examination could easily be taken for fibroma and unquestionably have been in the past. Solitary xanthoma, xanthogranuloma, or lipid granulomatosis, is a diagnosis based on the concept that because foam cells are often present in fibroma of bone this criterion places the lesion in the lipid granuloma group. This tendency has been carried to the point where some investigators group eosinophilic granuloma, fibrous dysplasia, and Hand-Schüller-



FIG. 21. Nonosteogenic fibroma of bone. Note eccentric subcortical location.



FIGS. 22 and 23. Nonosteogenic fibroma.

Christian's disease together as variants of a single disorder. Of greater importance, however, is the mistaken diagnosis of fibroma for fibrosarcoma of low grade. An instance of this error occurred many years ago. The lesion



FIG. 24. Nonosteogenic fibroma of bone. Histologic appearance was suggestive of xanthoma.

was heavily radiated and much later required amputation for radiation osteitis and permanent skin damage. Even at the time, before any of the processes mentioned above had been described, the pathologist hesitated to classify this lesion as a fibrosarcoma (see Fig. 20).

Nonosteogenic fibroma of bone, being a benign and localized condition, lends itself to surgical removal either by thorough curettage or, in bones like the fibula, by segmental resection of the diseased area. Postoperative radiation seems entirely illogical and has not been used in any of Jaffe's cases. It would not be advisable to resort to it without a previous tissue examination to assure the correctness of the diagnosis. Moreover, there is no logical reason to anticipate that this tumor would prove radiosensitive (see Figs. 21-24).

9. CHONDROMA

TUMORS DERIVED WHOLLY OR IN PART FROM CARTILAGE INCLUDE THE following: exostosis, osteochondroma, hereditary deforming dyschondroplasia, Mafucci's syndrome (dyschondroplasia with hemangioma) and central chondroma.

EXOSTOSIS

This condition has already been described in connection with Osteoma (see p. 80).

OSTEOCHONDROMA.

These tumors arise in areas where cartilage is ordinarily found and project as nodular protuberances from, or are partially imbedded in, bone. They tend to project from a portion of the marrow cavity, extend through the cortex and appear as bulky masses. In some instances they may produce considerable distortion of the bone from which they arise. Many theories have been advanced as to their etiology, e.g., rickets, trauma, embryonic cell rests, etc. It seems probable that they are nearly always congenital in nature. Roentgenograms of these tumors frequently reveal irregular calcific deposits in the tumor mass where they project prominently against muscle groups. These may develop adventitious bursae, and calcareous material may also form within such bursae. Attachment to the shaft of the bone may be by a broad pedicle which merges with normal bone, both cortical and medullary. These tumors tend to be restricted to the pelvis and long bones, and in the latter they arise near the extremities of the shaft in the region of, or adjacent to, the epiphyseal line. In addition to those of the pelvis, other flat bones are occasionally involved (see Fig. 25).

CLINICAL COURSE

Osteochondromas may exist for many years or even throughout life with very little inconvenience and with no change in character but, when they are bulky or are located in such sites as the popliteal region, the upper inner aspect of the humerus, the clavicle, or scapula, they may occasion discomfort by reason of pressure upon nerves or blood vessels. In other

locations, too, they may present bulging prominences which are painful on physical exertion or may inconvenience the subject at his occupation. Under such circumstances or when their structure as seen on roentgeno-



FIG. 25. Osteochondroma of scapula.

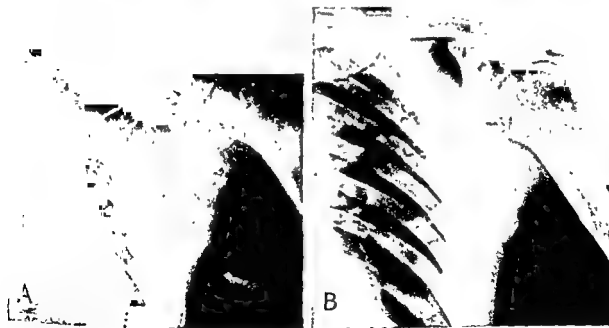


FIG. 26. A, Osteochondroma of scapula; B, same case after subtotal scapulectomy.

grams is grossly irregular or there is any indication of change in the size or of development of pain in the area, resection is definitely desirable (see Figs. 26-32).

Incomplete extirpation is to be avoided. Wherever possible the base



c. 27. A, Osteochondroma of upper fibula. Tumors of this size may produce increased pressure symptoms; B, same case showing appearance after partial resection of fibula with complete removal of tumor. (Parkland Hospital, Dallas, Texas)



FIG. 28. Multiple osteochondroma.



FIG. 29. Osteochondroma of tibia.



FIG 30 A, Large osteochondroma of scapula; B, same case after partial resection of scapula with complete removal of the tumor-bearing area. (Parkland Hospital, Dallas, Texas.)

should be removed and the normal bone cauterized to insure against leaving behind particles of tissue from which a recurrence or malignant metaplasia could develop.



FIG. 31. (left) - Sessile form of osteochondroma.

FIG. 32. (right) - Osteochondroma. This is the bulky type that frequently causes pressure symptoms.

"Injury to isolated chondromas may result," as Brailsford contends, "in rapid growth in which the structure of the affected bone may be completely broken up and its fragments carried away into the tumor mass. Localized resection usually results in a cure but in some cases sarcomatous metaplasia takes place and the patient dies from multiple secondaries." Films of an illustrative case personally treated are seen in Fig. 33, and see also Fig. 34. An extraordinary case is described in Chapter 65, p. 631.

HEREDITARY DEFORMING DYSCHONDROPLASIA

While most osteochondromas are single, there is a type in which deforming tumors occur throughout the skeleton and affect the bones that are derived from cartilage. Bowing of the long bones and distortion of the ends of the bones are frequent. This condition is known as hereditary deforming dyschondroplasia (see Fig. 35).

The familial character of multiple chondrodystrophies associated with skeletal abnormalities and deformities for which Ollier in 1888 suggested the name *dyschondroplasia*, deserves consideration in the group of tumor-like processes derived from cartilage.

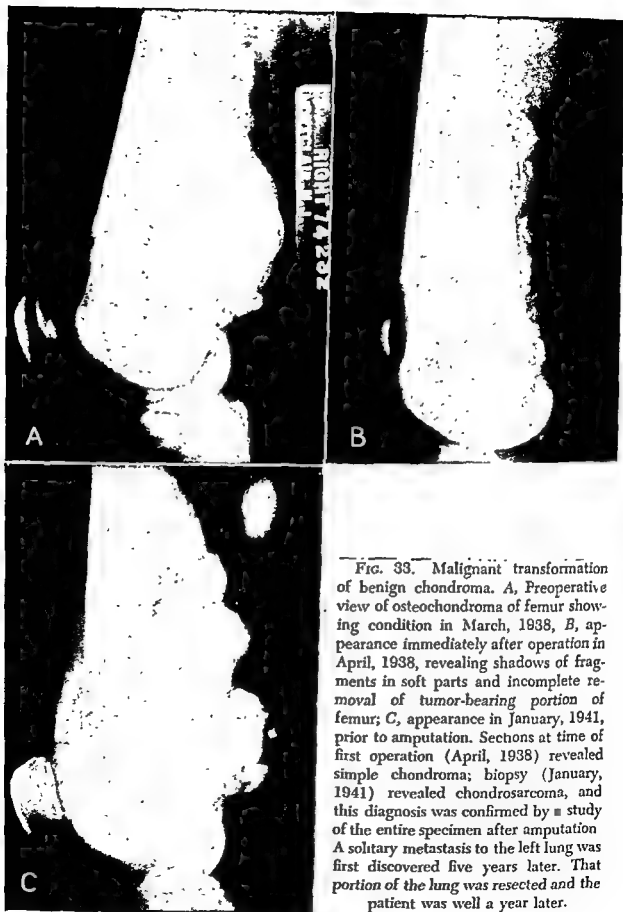


FIG. 33. Malignant transformation of benign chondroma. A, Preoperative view of osteochondroma of femur showing condition in March, 1938, B, appearance immediately after operation in April, 1938, revealing shadows of fragments in soft parts and incomplete removal of tumor-bearing portion of femur; C, appearance in January, 1941, prior to amputation. Sections at time of first operation (April, 1938) revealed simple chondroma; biopsy (January, 1941) revealed chondrosarcoma, and this diagnosis was confirmed by a study of the entire specimen after amputation. A solitary metastasis to the left lung was first discovered five years later. That portion of the lung was resected and the patient was well a year later.



FIG. 34. Multiple osteochondroma involving one extremity with secondary chondrocarcinomatous changes in the upper femur. This tumor extended into the pelvis and caused intestinal obstruction and, ultimately, the death of the patient. This is the type known as Ollier's disease.



FIG. 35. Multiple hereditary dyschondroplasia involving long bones.

Believing that the chief disturbance lay in the modelling or pruning of the diaphyses, Sir Arthur Keith in 1919 proposed the term *diaphyseal aclasis*.

In 1928 Jansen propounded a theory which Cohn believes fully explains all of the phenomena noted in connection with the condition. According to Jansen:

During growth the epiphysis is displaced distally by the growth disk, the metaphysis is not. It stands to reason that only if tubulation keeps pace with longitudinal growth of bone, will the normal funnel-shape of the diaphysis be close to the epiphysis; whereas an approximately cylindrical area of cancellous tissue produced by the growth disk must be expected to lie between the funnel-shaped end of the metaphysis and the growth cartilage when tubulation is retarded. Hence, the conclusion presents itself that the cylindrical or barrel-shaped area between the growth cartilage and the *funnel-shaped metaphysis* is caused by a retardation of tubulation and exostoses are the result of partial retardation of tubulation. These two phenomena appear to us to be the result of a total or partial dissociation through retardation of tubulation with regard to the other processes of longitudinal growth.

The familial nature of this condition is well recognized. We have seen it occur in twin boys and in a number of instances in more than one generation of the same family. Cohn cites an instance of the condition occurring in three generations and in another in two generations of the same family.

Heredity in dyschondroplasia was carefully studied by Vanzant and Vanzant as exemplified in a remarkable family. A man known to have had the disease married a cousin who also may have had it; they produced seven children all of whom were affected. The next generation had both normal and affected children. In later generations all the offspring of normal males were normal but 2 of the 3 normal females gave birth to affected as well as unaffected children. The affected males and females produced both normal and affected children in approximately equal proportions; in the affected families the ratio of normal to affected males was 15 to 1 and of females 15 to 17. These authors consider that the condition is transmitted as a Mendelian dominant.

Dyschondroplasia may be described as an hereditary retardation phenomenon affecting the metaphyseal areas of long bones but not primarily involving the epiphyseal. When deformities are noted in the epiphyses they are considered secondary changes. At times the shafts of the metacarpals and phalanges are affected. Although the disease is regarded as typically multiple there are numerous instances where only one bone is involved. At times this may produce marked deformity, as is seen when the condition involves the radius, and gives rise to Madelung's deformity (first described by Madelung in 1878). In addition to the multiple (bilateral) and solitary lesions one sometimes sees it occurring unilaterally and it may involve only the long bones of a single extremity.

The bone lesions are chiefly enchondromatous rather than osteochondromatous, and are characterized by irregular expansion of the cortex and widening of the shaft. Other long bones and flat bones are less commonly affected.

The vascular lesions seem unrelated and may occur only coincidentally and as separate manifestations of a mesodermal dysplasia. Inheritance, which plays a part in ordinary dyschondroplasia, does not necessarily affect the hemangiomatous element in this syndrome. Phleboliths may be demonstrated in the hemangiomas.

It is not unlikely that this condition occurs more often than reports would indicate. In all cases of dyschondroplasia the possibility of associated hemangiomata should be borne in mind. Treatment does not differ from that indicated for the uncomplicated dyschondroplasia, and the prognosis is the same.

MORQUIO'S DISEASE

In passing one should mention a familial skeletal dystrophy which was first described by Morquio in 1929. This condition is characterized by a generalized osseous dystrophy confined, however, chiefly to the skull and extremities as in achondrodysplasia. The head is large, the eyes widely spaced and the roof of the nose is depressed. Roentgenographic alterations are found in the skull and suture lines are absent. There may be optic atrophy and blindness.

The extremity bones show delayed epiphyseal development and distortion of the shaft of the phalanges, metacarpals and the metaphyseal areas of the bones of the arm and forearm. There may be a loss of ability to flex or extend the elbows and fingers. The calcium and phosphorus blood levels are normal.

CENTRAL CHONDROMA

The centrally situated tumors of cartilaginous derivation are known as chondromas, chondromyxomas, or enchondromas. It is well recognized that

TABLE IX
DISTRIBUTION IN TWENTY-TWO CASES OF CENTRAL CHONDROMA

BONE INVOLVED	NUMBER OF CASES
Phalanx	8
Femur	4
Tibia	4
Humerus	2
Fibula	1
Metacarpal	1
Rib	1
Multiple (phalanges, metacarpal, fibula)	1
	22

these growths occur in the metacarpals, metatarsals, and phalanges of the hands and feet, and in ribs, femur, tibia, humerus, and pelvic bones (see Table IX). The diagnosis from roentgenographic examination may be quite

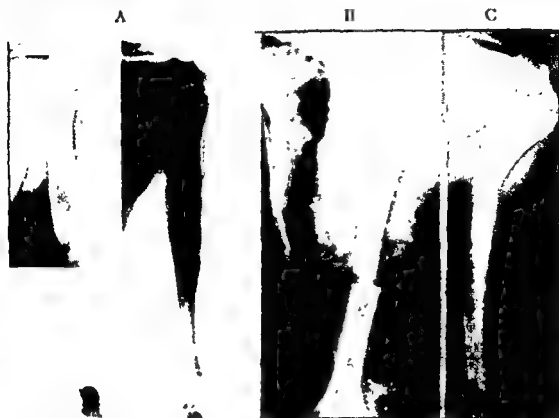


FIG. 36. A, Thrice recurrent central chondroma of humerus. Curettage failed to control disease. Lesion considered of borderline malignancy; B, segmental resection and substitution of a large tibial transplant with dowels for fixation. Note that no metallic fixation was used; C, view eighteen months following operation. Solid healing and excellent functional result without evidence of disease eleven years later.

difficult for they can closely simulate a giant cell tumor or a cyst, or even an osteolytic area due to a central sarcoma of low grade.

Though central chondroma undoubtedly has a long latent period before its presence is suspected it is most often seen between the ages of 10 and 30.

Their predilection for long bones, especially of an extremity is now well established (see Figs. 36 and 37). The preponderance of phalangeal chondromas is noteworthy; it is the most common tumor in the bones of the hand.

CLINICAL MANIFESTATIONS

Simple chondroma may be completely symptomless. When it has altered the contour of the bone the patient may notice swelling or deformity. Pain, when present, is generally inconstant and mild. Disability is infrequent. Pathologic fracture, especially in phalangeal chondroma, is often the incident which gives rise to the recognition of the condition. Trauma which results in the fracture is often trivial and nearly always less severe than that which is responsible for simple fractures through normal bone. There was

a history of antecedent injury in 8 cases which led to the discovery of the tumor. The usual history was that of an injury followed by pain, swelling, and ecchymosis. However, the triviality of the symptoms is indicated by the fact that the patients delayed several years before seeking treatment.

ROENTGENOGRAPHIC FINDINGS

While the roentgenologist can frequently make a strong presumptive diagnosis of central chondroma on the basis of a circumscribed area of radiolucency in the end of a long bone it is often possible to confuse the picture with that presented by bone cyst, giant cell tumor, and nonosteogenic fibroma of bone. We have seen cases in which a roentgenographic diagnosis of giant cell tumor was made without biopsy and prolonged roentgen therapy given without apparent improvement, and ultimately the diagnosis of chondroma was confirmed by late histologic examination. By this time the effect of the radiation was such as to render surgical attack impractical or actually hazardous. We believe therefore that any accessible central bone lesion deserves exploration and complete extirpation by surgical means since this assures a microscopic diagnosis and the method

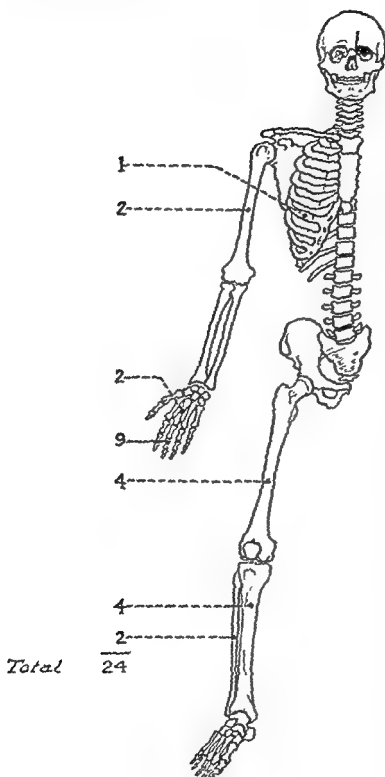


FIG. 37. Distribution of 24 cases of central chondroma.

gives satisfactory results regardless of whether it proves to be a cyst, chondroma or giant cell tumor. In certain instances a central chondroma may

closely resemble a chondrosarcoma or osteolytic osteogenic sarcoma and it is therefore imperative that this issue be clearly decided before radical surgery is instituted.

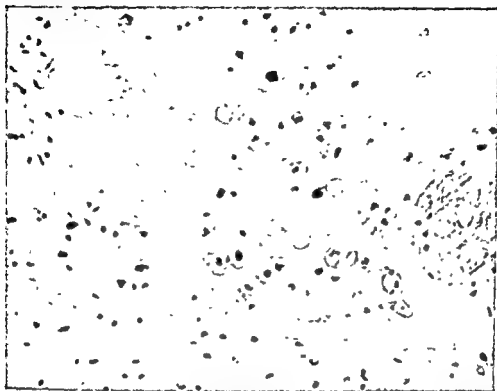


FIG. 38. Chondroma. Composed principally of adult cartilage cells. Slight nuclear variation in size and staining properties but at this level not a change of clinical significance.

GROSS APPEARANCE

The surgeon seldom finds it difficult to identify this tumor at operation. It lacks the gross appearance of tissue seen in simple cyst, giant cell tumor, or fibrous dysplasia. It presents a solid, whitish, firm tumor completely filling the cavity and has a slightly gritty feel when attempts are made to remove it with the curet. At times calcific particles are seen and felt but it lacks the purely fibrous quality of fibrous dysplasia, the vascular reddish nature of giant cell tumor, or the fluid-filled spaces of simple cyst. Myxomatous changes are not uncommon and it is probable that the extremely rare cases of pure myxoma of bone which have been reported are examples of degeneration of a central chondroma. While not encapsulated the lesion is usually rather definitely circumscribed and for this reason it is possible to remove it completely by painstaking curettage.

MICROSCOPIC FINDINGS

The histologic appearance of this tumor is so characteristic that it should offer little difficulty to the experienced pathologist. Hyaline cartilage predominates. The cells are usually rounded but may vary in size and may

become fusiform or stellate. Calcification may be seen in scattered areas (see Fig. 38).

Since there is a distinct tendency toward secondary chondrosarcomatous change and because this may not be evident in all parts of the tumor it is necessary to bear in mind that a report of "benign chondroma" based on an examination of only a portion of the entire tumor can be misleading. It is of course obvious that a microscopic study should invariably be made of all portions of the tissue removed from a central bone lesion.

TREATMENT

Treatment of chondroma is surgical; many observers have found them to be radioresistant. For localized osteochondroma, resection or excision is the preferred method, and it should be cleanly done with complete removal of all of the chondromatous area. For central chondroma of the phalanx, a complete excirpation, by means of careful curettage, of the tilage which fills the bone cavity, followed by chemical cauterization is the method of choice. There should be a bloodless field, adequate exposure, and care in avoiding the digital nerves and arteries. An incision is made on the side of the finger similar to that advocated for drainage of an infected tendon sheath but placed nearer the dorsum. The periosteum is then divided longitudinally and retracted to expose a rectangular area of cortex. As a rule the growth of the chondroma has resulted in a thinned-out cortex which may be readily divided by a small osteotome or even by a scalpel. Good exposure is obtained by removing a rectangular area of cortex which permits thorough curettage of the cavity until only firm cortical bone remains. Zinc chloride solution (saturated) on a small cotton-tipped applicator is swabbed over the entire surface of the bone cavity and allowed to remain in contact for one or two minutes, after which the cavity is freely irrigated with normal saline solution.

When the area of involvement is great and the cortical shell thin, it has been found desirable to fill the cavity with several matchstick grafts which are conveniently taken from the tibia. These are preferable to chips and result in a stronger reparative process; those preferring chips, however, generally take them from the crest of the ilium.

Careful layer closure of periosteum, subcutaneous tissues, and skin completes the procedure. A firm, even, compression dressing is then applied and the finger and hand splinted in the position of function. Dressing should not be disturbed for seven or eight days and sutures are removed at this time. The incision should be supported thereafter for at least another week for if this is not done the edges of the incision may tend to separate.

In rare instances there are encountered extensive chondromas involving a large area in a long bone, which are not suitable for resection or excision.

These cases present a definite hazard of malignant degeneration and occasionally amputation may be justified (see Fig. 40).

One cannot be certain on roentgenographic examination that the lesion



FIG. 39. Osteochondroma of tibia producing structural change in fibula due to long-standing pressure.

is still benign; in fact on a single biopsy specimen the report may be "chondroma" whereas other areas may reveal "chondrosarcoma." To reach a decision in such cases requires considerable judgment and involves great responsibility. One has an aversion to performing an amputation for a



FIG. 40. Diffuse chondroma of tibia. This case was amputated. The appearances suggest the likelihood of secondary chondromyxosarcomatous changes.



FIG. 41. Extensive enchondromatosis confined to a single bone in a 13-year-old female. Roentgenographic appearance is somewhat similar to that of fibrous dysplasia.

condition that has not reached the malignant stage and yet to postpone it until the sarcomatous properties are obvious may mean sacrificing the life of the patient.

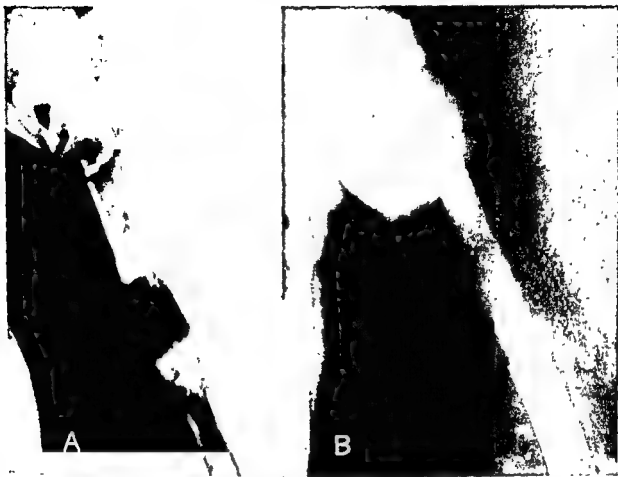


FIG. 42. A, Chondroma of humerus. Appearance after five previous operations; B, same case showing massive bone transplant used to bridge the defect after segmental resection.

Sometimes a central lesion in a long bone may be subjected to segmental resection and the defect bridged by a massive graft from the tibia or by utilizing the fibula. Phemister has resorted to this method with excellent results. A highly satisfactory example of segmental resection of the middle three-fifths of the humerus with massive tibial transplant is illustrated in Fig. 36, page 101. This procedure requires a careful selection of cases. It is applicable not only to benign chondroma but also to selected cases of low-grade chondromyxosarcoma or fibrosarcoma. The involved area must be distinctly localized and susceptible of wide removal without traversing tumor tissue at any stage. Bone must be provided in bulk commensurate with that of the segment removed (see Fig. 42). Phemister has used a bone graft from both tibiae in a case where a segment of the femur was resected. Transplanted segments attain a surprising resemblance to the shaft of the bone to which they are attached and take on its structure and function.

When operations are performed for chondromatous tumors there is a distinct tendency for the development of soft-part recurrences which often assume an ovoid or spherical form. Undoubtedly these represent implanta-



FIG. 43. Osteochondromatosis of knee-joint.

tion of tumor cells in the soft parts overlying the operative site. As a precautionary measure it is well to wall off the soft parts with pads moistened in saline solution and to irrigate the wound thoroughly prior to closure.

TABLE X
TREATMENT OF CENTRAL CHONDROMA*

METHOD	NUMBER OF CASES	
Roentgen rays only	0	
Surgery only	17	
excision		2
curettage alone		6
curettage plus chips or transplants		6
resection		2
amputation		1
Roentgen rays and surgery	4	
amputation		3
resection		1
Operation elsewhere	1	
Total	22	

* Memorial Hospital, 1947.

OSTEOCHONDROMATOSIS

Osteochondromas may on rare occasions be found in joint cavities, bursae, and tendon sheaths or attached to tendons and ligaments. Multiple small osteochondromatous masses may fill the joint cavities of the knee and shoulder; these have been termed *osteocondromatosis* (see Fig. 43). When an osteochondroma develops in a bursa the condition is known as *exostosis burcata*. However any projecting exostosis or osteochondroma may give rise to the formation of an adventitious bursa where movement of overlying muscles takes place.

Tumors of tendons may include osteochondromas; these may also arise within the tendon sheath near its point of insertion. Cases of this sort have been reported by Patel, Janik, Buxton, and Geschickter and Copeland.

OSTEOCHONDROSIS OF THE GROWTH CENTER

There is a group of closely allied lesions of the ossification centers in children which we find gives rise to symptoms, and at times even presents roentgenographic findings suggestive of bone neoplasms. While these disturbances of ossification centers may occur in a wide variety of localities, certain ones are commonly known under the names of the persons who first described them, for example, in the hip—Calvé-Legg-Perthe; in the tibial tubercle—Osgood-Schlatter; in the patella and tarsal scaphoid—Kohler.

Over a period of years a considerable number of these cases have been observed in the Bone Tumor Department of Memorial Hospital but in only a single instance was the diagnosis of malignant tumor considered seriously enough to warrant an operative biopsy.

IO. CHONDRODYSTROPHIA CALCIFICANS CONGENITA

AN EXTREMELY RARE CONDITION AFFECTING CHILDREN, WHICH IS FAMILIAL, congenital, and associated with calcareous particles lying in epiphyseal cartilages, was first described in 1914 by Conradi. It was first



FIG 44 · Chondrodystrophia calcificans congenita (see Vinke, T.H., and Duffy, F.P.: *J. Bone & Joint Surg* 29:511, 1947).

reported in America by Tisdall and Erb in 1924, and given its name, "chondrodystrophia calcificans congenita," by Raap in 1943. In 1947 Vinke and Duffy reported a total of 11 cases collected from the British and American literature and added 2 of their own.

The striking features of the condition are its stippled epiphyses, its congenital and familial tendency, and its association with cataract of congenital

CHONDRODYSSTROPHIA CAUCHICANS CONGENITA

type, as well as occasional other defects or abnormalities of development. Several examples of this condition appearing in siblings have been reported. It is a disease of infancy and most of the cases reported were discovered from 1 month to 2 years of age.

The diagnosis is made solely on the roentgenographic findings which are distinctive (see Fig. 44). Laboratory studies are not helpful and no serum phosphatase, phosphorus, and calcium readings have been reported.

Vinke and Duffy contend that stippled epiphyses without diffuse cartilagenous opacities within the cartilage and occurring in older patients represent a different entity from that present in their cases and the 9 of 10.

There may be some connection between this condition and some of the other congenital disturbances of cartilage development but this association is at present purely speculative.

II. BENIGN CHONDROBLASTOMA OF BONE

(Codman's Epiphyseal Chondromatous Giant Cell Tumor)

AMONG THE NOTEWORTHY CONTRIBUTIONS TO THE KNOWLEDGE OF BONE tumors made by Codman, founder and first registrar of the Bone Sarcoma Registry of the American College of Surgeons, is the identification of the tumor that bears his name as a distinct clinical entity.

Codman considered this tumor a variant of the typical giant cell tumor. Recent writers have objected to its inclusion with the giant cell tumors and believe it is a growth of cartilaginous origin. Jaffe, for example, maintains that the lesion develops from cartilage germ cells and should be termed benign chondroblastoma of bone.

Unquestionably the presence of giant cells in and about the tumor have misled observers. However, Jaffe points out that they occur only in those areas in which there has been considerable necrosis and hemorrhage or in areas of chondroid organization; moreover, they show a clumped arrangement, are somewhat larger in size than the tumor giant cells and are probably merely osteoclasts.

Clinically there is much to differentiate this tumor from giant cell tumor. It may affect younger individuals before epiphyseal closure, is less aggressive, and presents areas of calcification not noted in untreated giant cell tumor; furthermore, when first seen, this tumor is smaller and more mottled in appearance than the giant cell tumor. Histologically, according to Jaffe, "there is a very definite aura of cartilage about the whole tumor."

Stout, in a personal communication, states that he is convinced that this lesion is a definite entity and is neither a chondrosarcoma nor a variety of giant cell tumor. He is uncertain whether Jaffe's interpretation is correct. He continues as follows:

... I recall one case which developed in the upper end of the fibula in a female aged 48 years treated at the Presbyterian Hospital by resection of the upper end of the fibula. At the time I realized that it was not a giant cell tumor, it was 10 years from any other case.

ever before encountered and was struck by its close resemblance to the mixed tumors of salivary glands. It was composed of the same jumble of poorly developed fibrocartilage and peculiar rounded cells which characterizes those tumors but it lacked any recognizable epithelial elements and so I hesitated to come to any conclusion about it. But if this lesion is not a mixed tumor, neither is it any ordinary type of cartilaginous growth, for the mononuclear cells which characterize it are like no normal embryological chondroblasts, and the peculiar fibrocartilage which the tumor formed sparingly is certainly different from any hyaline cartilage formed by ordinary chondromatous neoplasms. Whatever this peculiar tumor may be it is probably due to some developmental fault or malposition of tissues. I reiterate, though, that I think you can accept it as an entity.

Geschickter maintains that this tumor, whose distinct identity he recognizes, is in reality a true sarcoma and refers to it as a chondroblastic sarcoma. However, we know of no verified instance where one of these tumors has metastasized and all of our personally treated cases have recovered after complete extirpation by curettage. Codman's series of 9 cases, followed from 10 to 30 years, were all well; Jaffe's 9 cases, followed for variable periods, were also well. It seems, therefore, that Geschickter's opinion that this lesion is a chondroblastic sarcoma lacks support in fact.

CLINICAL FEATURES

The age of the patient is of some importance since the condition occurs in a rather limited period from 12 to 25 years with an average of 16 years. There is a distinct predilection for the male sex which is affected in approximately 80 per cent of cases.

While Codman's original 9 cases, collected from the Registry, were all confined to the upper end of the humerus, it is now known that the lower femoral and upper and lower tibial epiphyses may be involved and the early impression that the upper humerus is the sole site of the tumor is now no longer held. Where the humerus is concerned, it should be mentioned that the epiphysis of the greater tuberosity is most prominently affected while that for the head itself is usually spared or but slightly involved.

SYMPTOMS AND SIGNS

The symptoms complained of are pain, swelling, and disability referable to the contiguous joint. There is a chronicity of these symptoms ranging from three months to a year or more. Trauma from a sprain, fall, or blow is mentioned as a possible causative factor, but this finding is not consistent and it more likely serves to attract the patient's attention to a condition that existed prior to injury. Local tenderness and slight elevation of surface temperature may be elicited. As in any other bone tumor, there may be some local atrophy of muscles.

ROENTGENOGRAPHIC EXAMINATION

These tumors present a rather characteristic appearance which usually permits a correct diagnosis after one has had an opportunity to see a few cases. The tumor occurs as an oval or rounded epiphyseal or juxta-epiphyseal process (see Figs. 45, 46, and 47). It may extend to the neighboring metaphysis; in such cases, the involvement is often eccentric and may expand the cortex. The tumor is rather sharply circumscribed and is not of large size. It has a distinctly mottled appearance due to calcific deposits in the cartilaginous tissue. This mottling is uneven. Surrounding the area occu-



FIG. 45. Benign chondroblastoma of bone.



FIG. 46. Benign chondroblastoma (giant cell tumor, cartilaginous variant) in a female aged 17, treated by curettage. Patient well eleven years.

pied by the tumor there is a condensation of bone such as is sometimes seen about an area of attenuated bone infection. Protrusion of the tumor may cause a bulging prominence; this was noticeable in 1 of our cases lo-

cated in the epiphyseal area of the tibial tubercle. As pointed out originally by Codman, this extension usually does not progress toward the articular surface to a point where cartilage is actually destroyed, yet Jaffe described

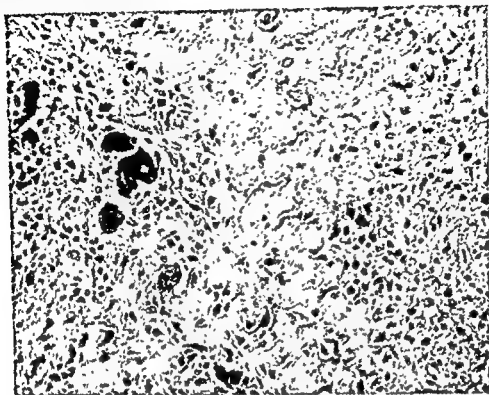


FIG. 47. Benign chondroblastoma. Histologically, the irregular cytology of this tumor might well tempt one to make a diagnosis of osteogenic sarcoma. Epulis-type giant cells are present and there is formation of osteoid and cartilaginous tissue. This is not a metastasizing tumor.

I case in which the articular cartilage of the humeral head was partially destroyed.

DIFFERENTIAL DIAGNOSIS

Prior to the time (1931) that the specific nature of this benign tumor of bone was first recognized it was most often mistaken for chondroblastic sarcoma, chondrosarcoma, or osteogenic sarcoma. In one instance an amputation was performed for a humeral tumor which proved to be typical of those later described by Codman. It is more than likely that others could be found in which the same mistake had been made. Roentgenologists have been quick to learn the distinguishing features of this lesion and such tragic mistakes will seldom be made in the future. It is situations such as this, though rarely encountered, that make it imperative that amputation for a supposed primary malignant tumor of bone should never be done without histologic proof of the true nature of the growth.

At times it becomes necessary to distinguish this tumor from a central

chondroma. This is not easy on clinical or roentgenographic evidence and the diagnosis must rest chiefly on histologic differences. Chondromas are composed of adult cartilage cells whereas chondroblastomas are derived from cartilage germ cells and do not take on the appearance of the mature cells seen in chondroma.

TREATMENT

Surgery is indicated and should be conservative. Curettage is the method of choice and should be thorough (see "Chondroma," page 104). It is followed by healing, and function should be excellent. Recurrence is unlikely. Radiation therapy is not necessary or advisable; when used in mild doses it may not do harm, but if heavy dosage is employed the effect on joint function may be undesirable. Combined use of both methods is deprecated. If radiation is used at all, it should not be in large doses and should not be given preoperatively. Surgical extirpation involves a meticulous curettage or a local excision of an eccentrically placed lesion.

PROGNOSIS

In general it may be stated that the outlook in these cases is excellent. The tumor is benign, yields to conservative surgical measures, and ultimate function is satisfactory. If left untreated, it would seem highly possible that secondary chondrosarcomatous degeneration might supervene in later life. Though this transition has never been proved, it seems not unlikely that some of the late chondromyxosarcomas of the upper humerus may have developed on the basis of untreated epiphyseal chondromatous tumors which had been present since adolescence. This is in keeping with our feeling that any untreated central cartilaginous lesion carries a threat of late malignant degeneration.

12. MYXOMA OF BONE

THE PAUCITY OF REPORTED CASES OF PURE MYXOMA OF BONE MIGHT BE construed as supporting the contention of some authorities that no such entity exists. While it is unquestionably among the rarest of primary neoplasms of bone, the cases recorded by Bloodgood and a few scattered references would appear to establish its existence.

Myxoma may be defined as a neoplasm of mesenchymal origin whose cells have a tendency to produce mucin, collagen, and fibroglia. It has a shiny, jellylike appearance and may be of almost liquid consistence so that it is difficult to pick up with forceps. Even after hardening in formalin it is exceedingly friable and difficult to section for microscopic study.

It should be understood that while pure myxoma of bone is distinctly rare, myxomatous areas are not uncommon in association with bone tumors of cartilaginous origin (chondromyxoma, chondromyxosarcoma) so that the term *myxoma* should therefore be reserved for tumors in which there is no trace of other cellular elements.

While myxoma is generally considered to be a benign tumor it has been recognized as having a marked tendency to recur and to metastasize. Bloodgood was probably the first to emphasize the seriousness of the ultimate outlook in this disease; he warned of the desirability of an immediate amputation once the diagnosis had been made and confirmed histologically. He affirmed the fact that in no other tissue was there greater danger of implantation of cells and subsequent local recurrence.

It is the author's belief that myxoma of bone is related to a degeneration of cartilage and that this explains why it is seen in tumors composed essentially of chondromatous or chondrosarcomatous tissue.

At all events, central myxomatous tumors or those combining chondromatous and myxomatous tissues should be dealt with along the lines advocated for central chondroma but with the knowledge that conservative measures must of necessity be extremely thorough and that it may be necessary to resort to more radical treatment if there is subsequent evidence of a recurrence. Moreover, expert pathologic interpretation of all tissues removed is required to avoid the danger of mistaking a myxochondrosarcoma for a myxoma.

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13. HEMANGIOMA OF BONE

TUMORS OF NEWLY FORMED BLOOD AND LYMPH VESSELS ARE TERMED angiomas. In bone, lymphangioma apparently has not been described. Though it may occur at any age and affect any bone, the most frequent site of hemangioma of bone is in the spine. Two types are recognized histologically: the cavernous, and the capillary or scirrhous. The former presents large spaces between which are bone trabeculae; the latter is composed of capillary (or slightly larger) blood spaces scattered throughout dense fibrous tissue with less numerous bony trabeculae.

HEMANGIOMA OF SPINE

According to Brailsford, if routine sections were made at necropsy, this would be found to be the most common lesion. Investigators have determined from large series of such examinations that it is present in 10 per cent of individuals autopsied. It appears to have a higher incidence with advancing years, e.g., 4.5 per cent under 20 years as compared with 36 per cent over 50 years. These figures may be misleading for the condition is seldom discovered roentgenographically during life.

One or more vertebrae may be affected, but in our experience the solitary form has been more often encountered. Though the outline of the vertebral body usually is altered but little, it may, particularly as a result of trauma, collapse with compression of the cord and terminate fatally.

Symptoms may be negligible, or consist of vague, transient pain of long standing referred to the spine. Diagnosis depends upon roentgenographic findings which are characteristic. There are vertical striations with lessened bone density between them (see Fig. 48). This is due to loss of the more delicate trabeculae and some absorption of calcium. The notable feature is the homogeneous and complete involvement of the entire vertebral body which alters its internal architecture while slightly widening its transverse diameter and narrowing its vertical depth without changing its general contour appreciably. It is of vast importance that a diagnosis be reached and treatment instituted before compression and resulting myelitis occurs.

TREATMENT

Irradiation has been used with good results. Two cases personally treated were relieved of complaints and have remained symptom-free for more



FIG. 48. Hemangioma of third lumbar vertebra. Note in the lateral view the compression of the body in the vertical plane and its expansion in the horizontal plane due to partial collapse.

than ten years. A spinal brace is considered a desirable precaution during the period of treatment and thereafter until bone regeneration is well established. As the process is not particularly radiosensitive it is necessary to give fairly large doses, but skin damage can be minimized by using a small portal accurately placed to include only the affected vertebral body.

HEMANGIOMA OF FLAT BONES

The cavernous angioma of flat bones is encountered but rarely. It produces a characteristic roentgenographic picture of radiating bone striae between which are areas of lessened density representing the cavernous blood spaces.

HEMANGIOMA OF LONG BONES

The roentgenographic appearance of these tumors, when they arise in long bones, is also quite characteristic: affected areas show rarefaction, expansion, and are circumscribed (see Figs. 49 and 50). Brailsford's classic description is excellent: "It has the appearance of a shaggy head of hair



FIG. 49. *Above*, Hemangioma of femur. This primary bone tumor is exceedingly uncommon in the long bones. (Case of Dr. Davis Spangler.) *Below*, Another case of hemangioma involving first metatarsal bone.



in which there is a centrum with coarse, slightly wavy, bony trabeculae radiating from it." Sometimes one bone may have two widely separate and distinct tumors.



FIG. 50. Microphotograph of cavernous hemangioma of bone.

Symptoms have usually been present for a long time and consist of swelling and dull aching in the area involved.

Treatment should be conservative, for radical surgical measures are seldom justified. Total or partial excision of a flat bone, where feasible, is a suitable procedure. Segmental resection of a long bone with bone transplant to bridge the defect is a method that has yielded excellent results.

14. SOLITARY BONE CYST (UNICAMERAL BONE CYST)

INTRODUCTION

THE DISEASE OF THE SKELETAL SYSTEM KNOWN AS SOLITARY BONE CYST should be distinguished from the variety which is generalized and due to hyperparathyroidism, and also from the disseminate form described first by Albright and later by Jaffe. As its name implies, the lesion is limited to a single focus in a single bone.

Bone cyst was first recognized by Virchow who in 1878 described a case found in the humerus at autopsy. Sonnenberg (1879) recorded a case of traumatic origin in an adolescent, and Schlange (1887) later described a similar case. Heineke (1903) was apparently the first to study this condition by means of roentgen-rays. Pfeiffer (1907) added to our knowledge of the histologic, bacteriologic, and roentgenographic features. In more recent times further contributions to the subject have been made by many authors including Bloodgood, Platou, Silver, Sisk, Geschickter and Copeland.

Solitary bone cyst is a definite clinical entity with well-recognized features. It has its onset in the period of childhood which is also the period of greatest activity in bone. In an active bone-tumor clinic only 52 cases have been seen in a twenty-six-year period, one must conclude that it is an uncommon lesion. It is seldom seen in an active phase after the age of 21; before the age of 4 it is rare. It has a striking predilection for the metaphyseal region of certain long bones, particularly the upper ends of the humerus and femur. These locations account for more than half of all cases (see Fig. 51).

The symptoms prior to fracture are mild or often nil, and 50 per cent of a group of patients studied by Higinbotham and the author were unaware of any abnormality until a pathologic fracture occurred. Moreover, in the cases without fracture, the duration of symptoms from onset to first admission was long, averaging two years. In some latent cases the interval

may be ten or more years. Patients may often recall a brief period of mild disability following an insignificant trauma which indicates a pathologic fracture that has healed promptly; in fact so complete and rapid is the healing that within a month or two it may be difficult to identify the actual position of the fracture line.

In bone cyst the entire course of the disease is in keeping with the essentially benign nature of the disease. It tends to increase in size slowly and to reach a relatively stationary stage which may persist for years. When fracture occurs, often as a result of the most trivial of injuries, rapid callus formation and healing of the fractured cortex by bony union usually takes place. Occasionally, as a result of a pathologic fracture, the cyst itself is healed by the laying down of new bone within the cavity. However, in most instances, such fracture results in only partial healing of the cyst and it is not uncommon for a second or a third fracture to occur.

CLASSIFICATION

The classification suggested by Bloodgood in 1910 *Total* has been followed by most subsequent writers on this subject. It is as follows:

1. Single cyst, bony shell, no connective-tissue lining
2. Cysts with a definite connective-tissue lining varying as a rule from 1 to 2 mm.

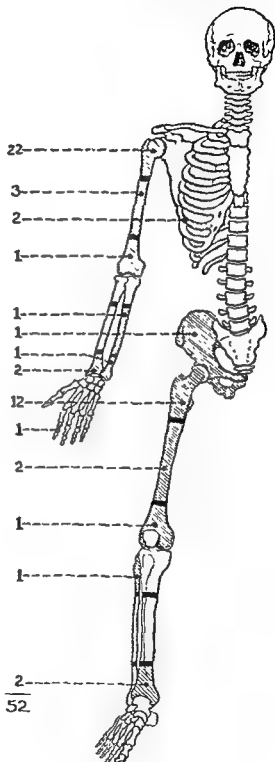


FIG. 51. Distribution of 52 cases of bone cyst.

3. A small cyst or cysts in a solid mass of osteitis fibrosa
4. No cyst, but bony shell filled with a solid mass of osteitis fibrosa
5. Multilocular cysts

This classification seems to be based mainly on the gross pathology as found at operation. The clinical significance of these separate groups is not apparent. They represent different stages of a pathologic process which probably begins with a subcortical hemorrhage followed in turn by localized bone destruction, a zone of vascular granulation tissue in which osteoclasts (giant cells) are found, then fibrosis, and later cyst formation. Ultimate healing is slow; a fact probably due to the difficulty with which a dead space is obliterated when its walls are rigid.

Unless a fracture has occurred, in no other disease of bone is the physical examination so devoid of clues to the nature of the underlying condition. The diagnosis practically always rests upon the roentgenographic findings. The area of osteolytic and expansile change is juxta-epiphyseal, although invariably on the diaphyseal side, with a well circumscribed, expanded cortex and often some trabeculation. The characteristic roentgenographic appearance is quite easily recognized and is confused only with giant cell tumor.

INTERMEDIATE FORMS

It appears that solitary bone cyst is closely allied to giant cell tumor, and that transitional or intermediate forms partaking somewhat of the nature of both are encountered. Tavernier describes in detail 3 cases personally observed which he terms "a bone disease intermediary between giant cell tumor and bone cyst." Geschickter and Copeland call attention to "giant cell variants of bone cyst," the chief distinctive feature of which, in their opinion, is the shorter period of symptoms, that is, six months or less.

We believe that the term *giant cell tumor* should be reserved for those cases which appear after the epiphysis has closed and in the juxta-articular region near the former epiphyseal line; while *bone cyst* should include only those cases that appear in this region before the closure of the epiphysis, and always on the shaft side of the epiphyseal line (see Fig. 52). To express it another way, *bone cyst* has its inception in childhood, *giant cell variant* during adolescence, and *giant cell tumor* after skeletal growth has been fully attained.

AGE

In the series of cases studied by Higinbotham, James, and the author, the average age was 15.3 years; the youngest were a boy and a girl of 3,

while the oldest was a male of 45. In Jaffe's series, 15 of 19 cases were from 3 to 14 years of age when the condition was first noticed; only 1 was a full-fledged adult at the time the condition first made itself felt.

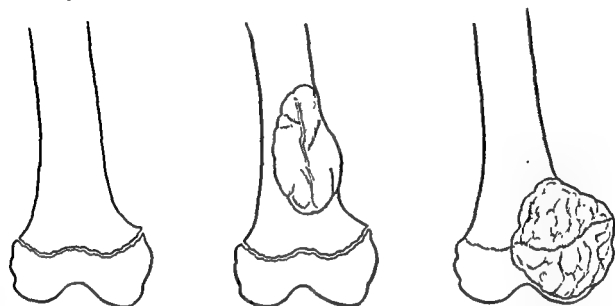


FIG. 52. Schematic drawing showing location in respect to the epiphyseal line of the involved bone area in bone cyst and giant cell tumor: left, normal femur; middle, bone cyst; right, giant cell tumor. Note that in the former the process is confined to the metaphysis while in the latter it crosses the epiphyseal line to involve the cancellous bone of the epiphysis.

SEX

Most writers agree that this condition is more frequently encountered in males. Our series contained 30 males and 22 females.

ETIOLOGY

As yet, no agreement has been reached concerning the etiology of simple bone cyst. Several theories have been advanced, some of which are briefly as follows:

1. *Theory of Trauma: Traumatic Hematoma*

This theory has attracted a number of writers. Jenckel, after studying 8 cases, reached the conclusion that bone cyst is often caused by hemorrhage. Lang held that a traumatic hematoma is the first factor in the development of a solitary cyst. Beneke also attempted to prove that a hemorrhage into the bone, which for some reason is not organized or absorbed, is the cause of cyst formation. Anshutz considered trauma to be an important etiological factor; Mauclair and Burnier regarded it as the most frequent cause. Platou, Mouchet, and LeGac opposed the theory of trauma, the latter two authors on the ground that all their cases showed well-developed cysts in a very short period after the trauma.

2. *Theory of Inflammation: Infection*

Bloodgood early adopted the view that osteitis fibrosa is primarily an inflammatory condition in which the medullary portion of the bone is replaced by connective tissue. Haeberlin believed that osteitis fibrosa is a circumscribed endosteal fibrogenous osteomatosis or an osteoplastic metaplasia of the endosteum with secondary fibrosis of the medulla associated with giant cell collections and degeneration of connective tissue secondary to these. He conceived that the process might be the result of a low-grade infection. Pfeiffer, after studying the histology, bacteriology, and roentgenograms of 4 cases, concluded that the circumscribed bone cysts are nothing but softening centers of inflammatory tissue in bone marrow.

3. *Theory of Metabolic Origin: Faulty Calcium Metabolism*

In their effort to determine the cause of the formation of bone cysts, some writers have been impelled by the evidence of malacia to attempt to show a relationship between bone cyst and Paget's disease in the adult and rickets in children. While Sisk holds that there is a fundamental change in the calcium metabolism common to all these conditions, he probably refers to the multiple form of osteitis fibrosa (Recklinghausen's disease) which is a distinct clinical entity and is not to be confused with solitary bone cyst. We believe that metabolic disturbances play no part in the etiology of bone cyst. Fujii considers osteitis fibrosa cystica as totally distinct from and independent of osteomalacia.

4. *Theory of Abnormal Hyperplasia of Osteoclasts: Progressive Osteoclastasia*

This theory, advanced by Geschickter and Copeland, concludes that bone cyst and giant cell tumor are results of an abnormal hyperplasia of osteoclasts. This is preceded by a normal stage in which osteoclastic proliferation is taking place as a step in the histogenesis of bone that is developed from preformed cartilage. They suggest the term *progressive osteoclastasia* for the process in giant cell tumor, and *regressive osteoclastasia* in bone cysts. They support their view by showing that where giant cell tumors are found they are situated where osteogenesis in cartilage is possible. Their theory invokes that of trauma in that it depends upon a traumatized subcortical area in which there has been an interruption of the blood supply from the periosteum to the cortical bone with the development of a subperiosteal hematoma. The medullary circulation in the region of the epiphysis must, by increased activity and establishment of new channels around the injured area, undertake the function of repair. This increased activity, however, occurs during a period when the cortical bone, cut off from its circulation, is undergoing necrosis. Thus an unequal balance is struck between bone destruction (osteoclasts) and reparative new bone

formation that would follow from reactive cortex if the circulation were intact.

5. *Pommer's Theory—Intramedullary Hemorrhage*

This theory has much more to recommend it although it is based on an histologic study of only 1 case. It assumes that solitary bone cyst results from encapsulation and alteration of a focus of intramedullary hemorrhage. It is believed that after the affected area has been encapsulated, transudation of fluid into it distends it. This distention and subsequent pressure interferes with the blood and lymph channels about it, causing erosion and later expansion of the adjacent cortical bone. Since fracture would remove the possibility of developing a closed pressure cyst, the occurrence after mild trauma without fracture but with associated hemorrhage in the medullary portion of the bone is said to be necessary for the development of bone cyst on this basis.

6. *Theory of Origin in a Bone Infarct*

This theory is similar to that of Pommer and differs chiefly in that it assumes a rarefying osteitis and eventual bone absorption occurring in a localized area of infarction of bone due to some aseptic interruption of its arterial blood supply. Cystic lesions, however, do not follow the aseptic necrosis caused by known infarctions, such as those seen in caisson workers.

7. *Local Post-traumatic Dystrophy*

Mikulicz maintained that solitary bone cyst represented some local disturbance in bone growth, i.e., a local post-traumatic dystrophy.

Jaffe has ably explained the connection between the location of the cystic area in relation to the epiphyseal plate and the activity or the latency of the individual cyst. Where the cyst is in contact with the cartilaginous epiphyseal plate, he regards the lesion as active and possessing capabilities for continued growth. However, where there is a zone of normal appearing bone between the epiphyseal plate and the margin of the cyst, the latter is in its latent or inactive phase. Although it may persist indefinitely, it is quiescent and does not thereafter extend or progress.

Jaffe feels that cysts in this phase heal most promptly after curettage and bone implants. However, we have noted that cases with no intervening normal bone between the cystic area and epiphyseal plate have not infrequently recurred after thorough curettage. It is in these cases that bone implantation in addition to curettage is most essential.

SUMMARY OF ETIOLOGY

There is no single accepted theory to account for the development of solitary bone cyst; each one that has been offered lacks conclusive evidence in support of it and is open to objections. The proponents of the traumatic

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SUMMARY OF ETIOLOGY

There is no single accepted theory to account for the development of solitary bone cyst; each one that has been offered lacks conclusive evidence in support of it and is open to objections. The proponents of the *traumatic*

theory fail to explain those cases which give an insidious history and are not associated with a definite injury. One must concede that trauma is an important factor in calling attention to an abnormal condition of bone; it is usually responsible for at least a partial fracture, and subsequent films made of the latter will reveal the presence of a well developed cyst. It seems clear then that trauma is frequently the exciting factor in the recognition of a cyst; it is by no means certain that it initiates it.

There is little scientific basis for the assumption that a calcium deficiency is the underlying cause. In 5 cases blood-calcium determinations were made and were within normal limits in each instance. In none of these did any other bone become involved in the cystic process. No dietary deficiencies have been established as existent in cases in this group.

As for the inflammation theory, the presence of an infectious or toxic agent has never been established. Bacteriologic studies have been unsuccessful in furnishing evidence of a causative organism, yet the histology and clinical course would seem to lend support to the supposition that a low-grade inflammatory process is responsible for the development of a bone cyst. On the other hand, the picture differs in most instances from that of a Brodie's abscess which is known to be due to a low-grade central osteomyelitis. While noting that it more closely resembles a healing process in its varying stages, one is led to ask what evokes the need for bone repair?

The conception of Geschickter and Copeland is based upon the known facts of blood supply, of bone repair, and of bone absorption by osteoclasts, yet it does not explain those cases in which there has been no trauma nor does it take into account the fact that while most children sustain many injuries of a minor nature to the growing ends of their long bones, bone cyst is a relatively uncommon finding among them. The same may be said for giant cell tumor in the young adult. Nor does their theory account for the relative rarity of bone cyst in the lower end of the femur, a most frequent site for giant cell tumors.

It must be admitted that none of the theories of the origin of bone cyst thus far is entirely convincing.

CLINICAL FEATURES

SYMPTOMS AND PHYSICAL SIGNS

Absence of pronounced symptoms is the rule for uncomplicated cases of solitary bone cyst. Pain is the most common complaint but even this is often so trivial and intermittent that it fails to arouse the patient's suspicions and a long interval is allowed to elapse before medical advice or treatment is sought. The pain may be felt after prolonged function or after a slight strain.

Pathologic fracture is frequently the first symptom. It was obviously

the initial symptom in 21 of the cases in our series in which there was a definite history. In a child, the occurrence of a fracture of a long bone near a joint following a trivial injury should arouse immediate suspicion of the presence of a bone cyst.

Swelling
tumor and
less the c,
nient position, such as the lower end
of the radius, ulna, or upper tibia.



FIG. 53. Bone cyst of upper humerus.



FIG. 54. Bone cyst of radius.

Disability is mentioned in the histories of only 2 of the 17 cases prior to fracture. Obviously it is complained of by all the patients in whom a fracture has occurred but it rapidly disappears with the healing of the fracture.

ROENTGENOGRAPHIC APPEARANCE

Bone cyst has certain well-defined characteristic roentgenographic features (see Figs. 53-61). Among these may be mentioned those noticed in the metaphyseal region, i.e., a decided thinning of the cortex with expansion (usually slight in degree) with an intact shell unless a pathologic fracture has occurred. In cases that have sustained one or more fractures, the subsequent healing frequently is associated with dense new bone formation which may traverse the cystic area in one or more trabeculations. While it is rather difficult to describe the roentgenographic picture, a study of a considerable number of typical films of solitary bone cyst will enable one to recognize the condition when it is encountered. It may simu-

late in appearance a giant cell tumor; however, it occurs in younger individuals and almost always before the adjacent epiphysis has united. It should be especially emphasized that bone cysts commence in the epiphysis on the diaphyseal side of the epiphyseal line whereas giant cell tumor begins on the joint side. Latent bone cysts, recognized in later life, may be found in the middle third of the shaft.

PATHOLOGY

The gross appearance seen when a bone cyst is opened varies consider-



FIG. 55. Bone cyst of femur.

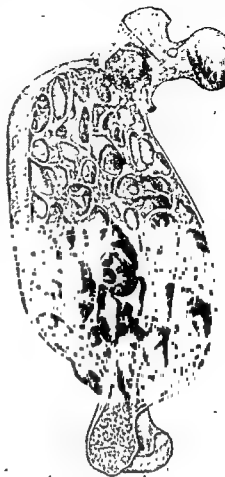


FIG. 56. Multilocular cysts developed in the body of the femur. Nélaton—see Bibliography.)

ably in cases which from the clinical and roentgenographic standpoint be quite similar. In many instances the cavity in the bone is not filled with fluid but contains a fine fibrous tissue network in which small space cysts are contained; in fact, the finding of a single cyst lined with fibrous tissue and completely filled with clear fluid is rather the exception than the rule. At times the content of the cavity may be grossly indistinguishable from that ordinarily seen in giant cell tumor but seldom does it possess the extreme vascularity so often characteristic of the latter disease.

Geschickter and Copeland made a rather extensive comparison of the pathology of bone cyst and giant cell tumor. They termed the former "progressive osteoclastasia" and the latter "progressive osteoclastasia" (see 126). However, few investigators since then have accepted their terminology.

It is our belief that bone cyst and giant cell tumor are closely connected.

conditions which have more than mere roentgenographic and histologic similarity to suggest this relationship. We have operated upon several typical bone cysts in which the microscopic appearance of many areas was quite typical of osteitis fibrosa while that of others presented a structure found in typical giant cell tumors. This difference would be a matter of greatest import were the diagnosis permitted to rest solely on histologic grounds. That this thought is by no means new is apparent from a remark made by John B. Murphy as early as 1913: "In fibrocystic disease the diagnosis may as well be made by the X-ray examination as by the microscope. The surgeon who depends upon frozen sections for diagnosis in bone tumors of central origin will come to grief."

We believe that the essential differences between bone cyst and giant cell tumor lie in the age of the patient and in the location of the lesion. The phase of bone destruction in the epiphysis meets with less resistance and evokes a less aggressive healing phase (defensive reaction of cortical bone) than it does in the metaphysis. It is more active in the young adult than in the child. Whether this is due in part to the fact that there is a more active bone reparative function in



FIG. 57. Bone cyst of lower tibia. Note its extension distally to the epiphyseal line.



FIG. 58. Cyst of os calcis.

the growing child than is present in the young adult, or solely to the fact that before the epiphyses have united the lesion attacks the metaphysis and is prevented from involving the epiphysis by the presence of the carti-

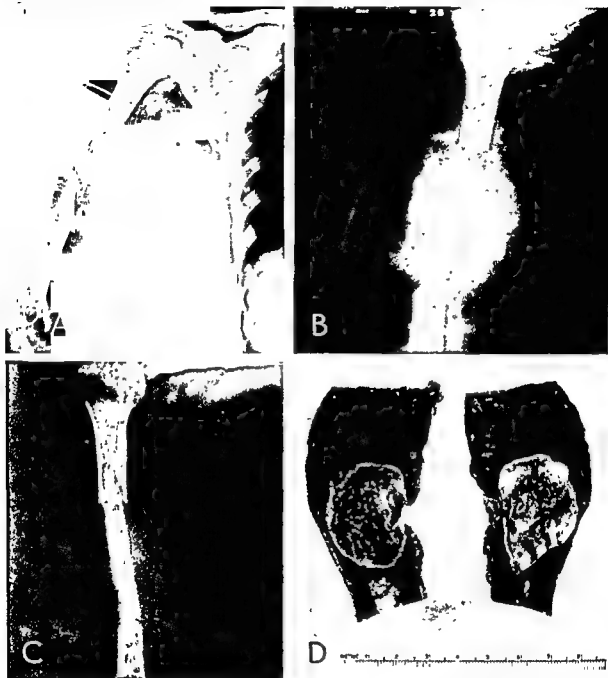


FIG. 59. A, Cyst of humeral shaft which recurred after two curettages and tibial transplants; B, same case immediately after segmental resection and massive substitution by tibial transplant; C, same case four months after operation (note that the transplant shows roentgenographic evidence of viability); D, gross appearance of the resected portion of the humerus.

lage layer at the epiphyseal line, is a matter of speculation. Whatever the explanation, it is a fact that in the metaphysis the arrested lesion, bone cyst, occurs; whereas in the epiphysis the progressive or unchecked lesion, giant cell tumor, is found.



FIG. 60. A, Cyst of the upper femoral shaft; B, postoperative view showing cortical transplant introduced into the cavity after curettage; C, final result five years after operation.



FIG. 61. Left, Bone cyst of humerus in a middle-aged male; right, same case five months after operation consisting of curettage and bone transplant to fill the cavity.

TRAUMA

The onset of symptoms following a trivial injury associated with a pathologic fracture is common; there is a history of trauma in about two-thirds of all cases.

DURATION OF SYMPTOMS

The majority of patients apply for medical attention early because of fracture; about one-third of all cases seek treatment within the first week after the onset of symptoms. These are the cases in which the pathologic fracture has aroused suspicion of the existence of a tumor. Those patients who do not suffer pathologic fracture may, due to the mildness of their symptoms and lack of disability, postpone medical attention for one year or as long as twenty-one years.

BONE INVOLVED

The upper femur, upper humerus, lower radius, upper tibia, upper fibula, and lower ulna are the sites of predilection for bone cysts. They may occur in the ribs, phalanges of hand or foot, pubis, and ischium. They are rarely found in the flat bones.

DIFFERENTIAL DIAGNOSIS

The differentiation of solitary bone cyst from other lesions of the skeletal system is not difficult. Few conditions present features even remotely similar to those of a typical cyst. The only circumstances under which there might be some reasonable doubt are those unusual ones in which a cyst has persisted into adult life. Here the condition may extend well away from the end of the bone, even approaching the middle third, and incomplete reparative changes may have altered considerably the roentgenographic appearance. Bone cyst gives rise to little, if any, discomfort except in cases where fracture has taken place. This, in conjunction with its orderly appearance on X-ray films and its relatively slow growth rate, points to a benign process. The reactive margin of bone seen in Brodie's abscess is lacking, whereas the marked tendency to symmetrical expansion and thinning of cortex is characteristic.

The one lesion resembling bone cyst in some respects is giant cell tumor. However, the position of the latter in respect to the epiphysis differs in that it nearly always begins in the epiphyseal end of the bone reaching the shaft later on by expansion. Finally, giant cell tumor and bone cyst occur in different age groups, and there is not much overlapping of these groups (see Table XI).

TREATMENT OF BONE CYST

The treatment of solitary bone cyst is surgical. There is a definite accord on this point among the many who have contributed to our knowledge of

TABLE XI
DIFFERENTIAL FACTORS IN THE DIAGNOSIS OF BONE CYST

FACTORS	BONE CYST (1)	FIBROUS DYSPLASIA (2)	HYPERPARATHYROIDISM (3)	CHONDROMA (4)	SARCOMA (5)	GIANT CELL TUMOR (6)
Age	5-18	Any age	Adults, particularly young & middle age	Adults	Any age	20-40
Location	Metaphysis	Not confined to any one portion of bone; often polyostotic	Generalized usually in diaphysis	Epiphysis or metaphysis	Epiphysis or metaphysis	Epiphysis
Bone involved	Upper humerus, upper tibia, upper femur	Any long or flat bone	Any long bone	Phalanges, femur, tibia, humerus	Femur, tibia, humerus	Femur, tibia, humerus
Fracture	Frequent (50%)	Rare	Frequent	Infrequent except in phalanges	Frequent (20-25%)	Less early but in 25%
Gross appearance of tissue	Multifocal serous, tissue is pale	Homogeneous; often of a rubbery consistence	Multifocal, fibrous	Homogeneous, pearly-white, looks like ice	Homogeneous, yellowish white or gray	Friable, vascular, reddish or brownish
Giant cells	May be present	Absent	Often present	Absent	Generally absent	Present
Vascularity	Avascular	Avascular	Avascular	Avascular	Moderate to slight	Plentiful
Röntgenographic appearance	Typical	Variable; may resemble bone cyst but is not in same location	Typical	May resemble giant cell tumor	May resemble giant cell tumor	Very vascular, even telangiectatic
Chemistry	Normal phosphorus, calcium, phosphatase	Phosphatase may be elevated	Calcium & phosphatase elevated moderately; phosphorus diminished	Normal values	May show normal values or elevated phosphatase	Normal phosphorus, calcium phosphatase
Pain	Trivial unless fracture	Slight to moderate; may be absent	Not very severe unless fracture	Usually mild or absent	Considerable	Slight to moderate
Swelling	Usually slight or absent	Usually inconspicuous	Depends on deformity of associated fractures	None or very slight	Usually some present	Not early, moderate late
Disability	May be some	Slight	Slight unless there is fracture	None unless fracture or in advanced stage	Usually none in early stage	Mild at first; marked if pathologic fracture

the disease; among these may be mentioned Haberer, Hoffmeister, Schlange, Tavernier, Mouchet, Dujarier, Heitz-Boyer, Fevres, Bloodgood, Sisk, Painter, and others. Sisk states, "In the treatment of osteitis fibrosa cystica the greatest economy of time is served by conservative surgery at the time the lesion is discovered. The uniform success obtained by surgery with a comparatively short convalescence period, argues against long periods of watchful waiting." While all agree that conservative surgery is indicated, there is apparently a wide range of procedures suggested, some of which cannot be regarded as conservative.

When a fracture has occurred in a previously unrecognized bone cyst, manipulation to obtain satisfactory position and immobilization during the healing period is in most cases all that is necessary to obtain prompt union. Yet the uncertainty of the ultimate effect of fracture on healing of the cyst makes it inadvisable to rely upon it; we prefer to operate regardless of the fracture.

TECHNIC OF OPERATION

Surgical interference consists in exposing the involved area, cutting a sufficiently large window to give access to the entire cavity and carefully curetting the entire contents down to cortical bone. The cavity should then be swabbed out with an escharotic, e.g., phenol and alcohol or zinc chloride (saturated solution), followed by irrigation with normal saline solution. The rectangular segment of cortical bone removed in exposing the cyst may then be placed in the cavity and in layers without drainage. Manual closure of the bone wall is desirable.

The practice of packing the cavity of a bone cyst (or any noninfected bone cavity) with gauze or drains of any sort cannot be too strongly condemned. Most of the surgical catastrophes have been due to infection following this procedure. When the wound has been properly closed in layers, the cavity fills with blood clots into which osteoblasts later migrate and form new bone. Unlike hematomas elsewhere, the blood clot in a bone cyst or a giant cell tumor cavity rarely becomes infected if the wound is properly closed. When packing is used, infection is apt to occur.

Most surgeons utilize chips of cancellous bone from the iliac crest to fill the cavity after curettage so that more complete and more rapid bone regeneration will take place. For extensive defects in the shaft of the long bone, larger rectangular grafts taken from the tibial cortex by means of a twin-bladed motor saw are sometimes to be preferred.

Occasionally cases are encountered in which failure on the part of repeated curettage and bone chips necessitates a consideration of segmental resection. The following is cited as an example:

CASE REPORT

D.F., male, aged 30 years, was admitted on Dec. 21, 1939, complaining of pain in the right shoulder of twelve months' duration. He gave a history of three episodes of traumatism to this area followed by pain. After the initial incident a fracture through a bone cyst was revealed. On examination the right arm appeared swollen over the mid-portion. There was pain on attempted motion in any direction. The left arm had been amputated following an accident at the age of 8. The diagnosis following an aspiration biopsy on January 3, 1940, was that of "wall of bone cyst." Operation on the same date consisted of curettage of the cyst and implantation of a bone transplant from the tibia. Fairly satisfactory bone regeneration took place and the patient remained well until June 5, 1943, when, on account of a recurrence of symptoms, a second operation was performed. This paralleled the first one. There was an additional period of three years of freedom from symptoms followed by a recurrence and roentgenographic evidence of reactivity. A segmental resection was performed on Apr. 8, 1946; a massive tibial transplant was dowelled to fit in the medullary cavity at either end. (see Fig. 59, p. 132). In Aug., 1946, the transplant was fractured in its mid-portion. Examination in January, 1947, revealed definite evidence of callus formation; while solid bony union at the fracture site was lacking, the proximal and distal ends of the transplants were firmly united to the shaft.

ROENTGEN THERAPY

While this form of therapy is employed for the treatment of bone cyst and has been followed by healing of the cystic area with satisfactory bone regeneration, it is generally considered inadvisable to use roentgen-rays in preference to surgery for lesions in accessible locations. This is particularly true in cases involving the ends of the long bones of the extremities, especially the lower. Retardation of bone growth as a result of damage to the epiphysis from the effects of roentgen therapy has been observed not only in animals but in many children as well. This has resulted in shortening of the affected bone. Of more serious significance is the danger of delayed development of sarcoma in the irradiated area (see p. 531).

PROGNOSIS

There is no danger to life nor necessity for mutilating operations; the prognosis for both life and limb is excellent. We have not had a death in our experience nor do we know of any. Fracture seldom produces much deformity and healing thereafter is usually prompt. There were no instances of nonunion or delayed union. If the fracture reoccurs there may be a sufficient loss of substance to create a slight, sometimes an appreciable, shortening, although this is unusual. In the upper extremity this may be of little or no significance, but in the upper femur with resultant coxa vara the shortening may be sufficient to require some compensatory measures. In lesions of lower extremity bones weight-bearing should not be

permitted until the bone repair is solid thus avoiding the risk of any serious deformity as a result of bending during the healing phase.

In 1934 Higinbotham and the author published a series of 26 cases of solitary bone cyst observed at Memorial Hospital between 1920 and 1935 inclusive. A study of the end results shows the following: Curettage with or without additional procedures was the method employed in 13 cases with 1 fair and 12 good results. Treatment of the fracture alone gave good results in 4 cases. Irradiation alone or combined with other procedures was used in 8 instances with 5 good results, 2 fair, and 1 not traced.

The end results of another group of 26 cases of solitary bone cyst observed at Memorial Hospital between 1935 and 1945 inclusive have recently been studied by James, Higinbotham, and the author. Surgery was the method employed in the entire group. In every instance the wound healed by primary union and there were no late imperfections in wound healing. A recurrence took place in 4 instances while the cyst-bearing area healed satisfactorily in the remaining 22 cases. Two of the 4 recurrences had another recurrence; all eventually healed save 1 in which the second operation had not yet been performed. The results in the entire group of 52 cases are shown in Table XII.

TABLE XII
RESULTS IN A SERIES OF 52 CASES OF BONE CYST*

TREATMENT EMPLOYED	RESULTS			
	Good	Fair	Poor	Not traced
No treatment	0	1	0	1
Treatment of fracture only	4	0	0	0
	13	1	1	0
	5	0	0	0
	12	2	2	0
	1	0	0	0
	2	0	0	0
Radiation alone	2	1	0	1
Radiation—later fracture—malunion requiring osteotomy	0	1	0	0
Resection	1	0	0	0
Curettage plus graft plus later resection	0	0	1	0
	40	6	4	2

* From the author's service, Memorial Hospital and Hospital for Special Surgery

It is our impression that cases in which bone transplants are used to fill the cavity have more complete and more certain bone regeneration with ultimate obliteration of the cavity than do those in which curettage alone is employed. The older the patient the more important it is to use bone transplants since the natural regenerative powers of bone seem to be less marked in later life.

Roentgen therapy, if employed at all, should be used in small doses and adequate protection should be afforded the adjacent epiphyseal line. In cases where the cyst extends close to this line such precautionary measures

are only partially successful. There is danger of retardation of bone growth when the epiphyses of growing children are irradiated. Of more importance is the occasional development of sarcoma in the cystic area exposed to roentgen therapy. We have encountered 3 cases in which after a lapse of from ten to fourteen years following roentgen therapy a sarcoma developed in the treated area. One of these patients died of pulmonary metastasis; one has survived an interscapulothoracic disarticulation and is well more than ten years, while the third recently underwent an interscapulothoracic disarticulation and the ultimate result is uncertain. As a result of our experience in the treatment of this condition we have abandoned roentgen therapy save for cases occurring in inaccessible locations; in fact, in none of the latter group of 26 cases did we employ roentgen therapy.

Allredge studied 152 cases of bone cyst collected from several large series and from individual orthopedic surgeons. He was concerned chiefly with the end-results of treatment by various methods. These cases when analyzed fell into the following categories:

1. No treatment except for pathological fracture when present (22 cases)
2. Irradiation alone (15 cases)
3. Irradiation combined with surgery:
 - a. Cases in which surgery was resorted to because of unsatisfactory results from irradiation (8 cases)
 - b. Other cases in which irradiation was used, preoperatively or postoperatively (10 cases)
4. Surgery:
 - a. Amputation (7 cases)
 - b. Resection or osteotomy, sometimes combined with bone grafts (15 cases)
 - c. Curettage alone as primary treatment (36 cases)
 - d. Curettage and cauterization (21 cases)
 - e. Primary curettage and the use of bone chips (9 cases)
 - f. Secondary curettage and the use of bone chips (5 cases)
 - g. Primary curettage and the use of a massive graft (15 cases)
 - h. Secondary curettage and the use of a massive graft (13 cases)

Allredge graded the results in all cases and some of the conclusions reached by him were as follows.*

There is definite evidence that surgery is less satisfactory after irradiation than when it is done alone. There is no operative or postoperative irradiation is of any benefit. Epithelioid sarcoma was fairly common in this group and a malignant change took place in two cases many years after irradiation had been used. [These were the only ones noted in his series—Author.] From this it is no doubt that better results were obtained when transplanted

* ALLREDGE, R. H. Localized fibrocystic diseases of bone. *J. Bone & Joint Surg.* 1942.

cavity than when no bone was transplanted into the cavity. The results of this study seem to narrow the choice of treatment in operable cases down to two methods—that is, resection, or the use of transplanted bone after thorough cleaning out of the cavity.

es, such as the
or most others.
here the lesion
has grown away from the epiphysis, resection and restoration of the shaft
by means of a massive bone transplant should probably be employed more
often.

15. FIBROUS DYSPLASIA OF BONE

CLASSIFICATION AND ETIOLOGY

DURING THE PAST DECADE, FOLLOWING THE PUBLISHED DESCRIPTIONS OF the disease entity now known as *fibrous dysplasia of bone*, cases have been more frequently recognized.

Goldhamer, Borak, and Doll in Germany; Lichtenstein, and Albright and his co-workers in America have described cases of this syndrome in different terms, e.g., "osteodystrophia fibrosa unilaterialis with pubertas precox," "polyostotic fibrous dysplasia," "osteitis fibrosa disseminata with areas of pigmentation and precocious puberty in the female." Phemister has applied the term "regional fibrous osteodystrophy."

Jaffe and Lichtenstein in 1942 reported a considerable number of cases with emphasis upon the accessory features as well as the osseous lesions.

The affection is probably a skeletal developmental anomaly characterized by single or multiple areas of fibrous tissue in bone. When multiple, it may be either unilateral or bilateral. The condition is usually recognized in childhood or early adult life, pursuing a slow and often inconspicuous clinical course and perhaps giving rise to deformity and swelling. Schlumberger, however, believes it probable that many of the monostotic cases represent a response to injury and quotes Hatcher in support of this theory.

To the author it has seemed probable that the term *fibrous dysplasia* is being applied to several forms of fibrocystic disease that may or may not be etiologically related.

The *first* of these is the classical polyostotic form with or without the associated areas of skin pigmentation and sexual precocity described by Albright and others.

The *second* is the monostotic form in which cutaneous and endocrine abnormalities are lacking. The likelihood seems strong that this process is closely allied to the first. Flat as well as long bones may be affected.

The *third* form, also monostotic, arises in a long bone of an extremity, occupies a wide area of the shaft, and resembles the solitary bone cyst of

childhood or adolescence which has progressed toward the diaphysis as a result of growth of normal bone. Undoubtedly cases in this category have in the past been termed bone cyst. Their roentgenographic appearance has justified the use of this term. There may be some connection between the late, untreated, quiescent bone cyst of childhood and the so-called fibrous dysplasia seen in the shaft of the long bones in adults. It would be interesting to follow untreated cases of unicameral bone cyst in children by repeated roentgenographic examination through adolescence and early adult life. Such a study might explain the cases presenting a cystic area in the shaft of long bones which are first detected in adult life.

The *fourth* is the eccentrically placed solitary lesion, usually in the metaphyseal area of a long bone, which Jaffe has termed "nonosteogenic fibroma of bone" but which some consider merely a variant of monostotic fibrous dysplasia.

Jaffe believes that while the overwhelming majority of the cases show only the dysplastic skeletal alterations with or without abnormal pigmentation, the small group that remains may be considered the fullblown form of the disease characterized, in addition to the skeletal and pigmentation features, by a tendency to precocious puberty, premature skeletal maturation, and at times hyperthyroidism and other disorders. The latter are generally termed examples of Albright's disease. Jaffe has estimated that the cases in which the skeletal changes occur alone outnumber those with precocious sexual development and marked pigmentation of the skin in the proportion of 20 or 30 to 1.

CLINICAL FEATURES

The disease is recognized most often in the third decade, although cases are now being seen more frequently in childhood and adolescence. Symptoms suggest that the average age of onset is at the end of the first or the beginning of the second decade. Women are affected more often than men in the ratio of 3 to 1. It appears to be a chronic disease, slowly developing but persistent throughout life. Common presenting symptoms are limp, deformity, pain, and pathologic fracture. The long bones are predominantly affected, although the skull, scapula, and pelvic bones have been found to be involved. The chronicity of the disease is attested by Lichtenstein's observation that the average duration of symptoms in his series was twenty years, and in 1 case thirty-six years.

Though one, several, or many bones may be affected, we believe that the monostotic form is much more common than either of the others. This would seem to be supported by the extensive series of Schlumberger who studied at the Army Institute of Pathology 67 cases of fibrous dysplasia involving a single bone, while in only 2 cases was more than one bone affected. These cases were all in individuals between 18 and 38 years. In

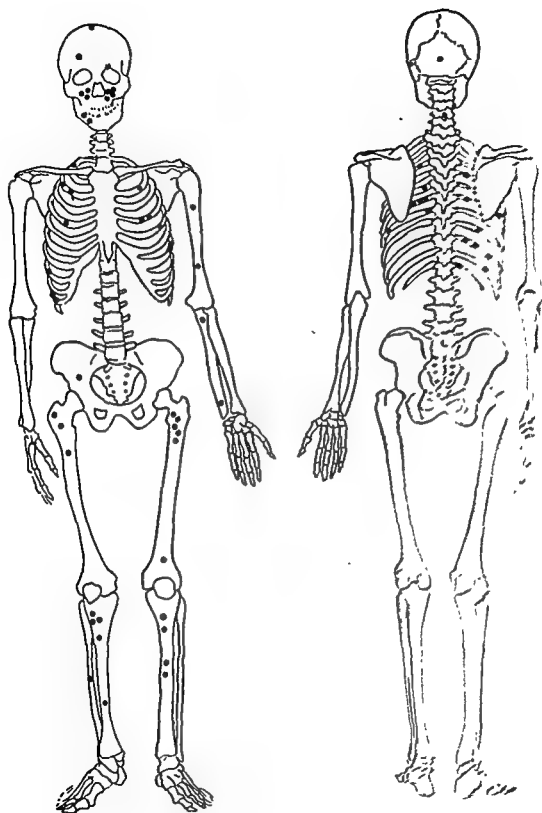


FIG. 62. Regional distribution of the lesions of monostotic fibrous dysplasia. Each dot on the skeleton represents a single instance (after *Spencer, 1964*).

none of these monostotic cases was cutaneous pigmentation or endocrine abnormality observed, nor were there any congenital anomalies.

The sites of predilection of the monostotic form may be seen from Schlumberger's figures on 67 cases as follows: rib 29, femur 9, tibia 8, maxilla 7, calvarium 5, mandible 2, humerus 2, ulna 2, vertebra 1, pelvis 1, fibula 1. The preponderance of rib lesions contrasts with the incidence of other varieties of bone tumors in which rib lesions form an inconspicuous percentage (see Fig. 62).

Albright has emphasized the triad of bone lesions, precocious sexual development in the female, and areas of skin pigmentation. In a case observed by the author, menstruation began at the age of 11 and was associated with fully developed secondary sex characteristics at the age of 8. The explanation of these skin and sex manifestations has not been established.

ROENTGENOGRAPHIC FEATURES

Fibrous dysplasia produces broadening or expansion of bone, thinning or erosion of the cortex, and a rarified multilocular or trabeculated appearance which is readily confused with other forms of cystic disease (see Figs. 63-69). Secondary deformities result from bending, or from pathologic



FIG. 63. Fibrous dysplasia.

fracture. When a single suspect lesion is found, roentgenographic examination of the entire skeleton should be carried out.

Conditions which may resemble fibrous dysplasia roentgenographically are Recklinghausen's disease, enchondroma, and bone cyst.

Jaffe has observed a large group of terms used in the literature to describe instances of what he considers were fibrous dysplasia, among which are "osteodystrophia fibrosa unilateralis, unilateral polyostotic osteitis fibrosa, unilateral Recklinghausen's disease, osteodystrophia fibrosa cystica generalisata limited to one side of the body, focal osteitis fibrosa, osteitis fibrosa in multiple foci, osteitis fibrosa with formation of hyaline cartilage and osteitis fibrosa disseminata."

The most frequent error in diagnosis made by roentgenographic examination is to consider the lesion as cystic disease on the basis of hyperparathyroidism. It is now apparent that on many occasions in the past cases of fibrous dysplasia were reported as instances of "cystic disease" or of Recklinghausen's disease. In the monostotic form of fibrous dysplasia the lesion may resemble a central chondroma or at times a giant cell tumor.

Chemical studies of the blood reveal that the serum calcium is usually normal, although slight elevations and depressions have been observed. Though inconstant, serum phosphatase elevations have been reported by



FIG. 64. Polyostotic fibrous dysplasia. Patient, young adult male. Note extensive involvement of ilium, ischium, and upper half of femur. Weight-bearing has produced coxa vara and some lateral bending of femoral shaft.

several observers. In 3 of Lichtenstein's cases the content was 17, 18, and 22 Bodansky units and 2 cases in Memorial Hospital had readings between 20 and 30 units.

It is important to exclude the diagnosis of hyperparathyroidism which has frequently been made on roentgenographic examination alone. Indeed, in at least 4 instances an exploration of the neck for parathyroid adenoma has been done for cases of fibrous dysplasia, and in 2 additional cases the neck has been radiated. The principal distinguishing features are the pre-

dominance of the disease in childhood, the frequent unilateral distribution, and the normal appearance of all of the unaffected bones which show no porosis. If there is reasonable doubt after careful study, it is advisable to



FIG. 65 Fibrous dysplasia. Note pathologic fracture without displacement. (Courtesy of D. Hart, Beckley, W. Va.)

perform a bone biopsy before subjecting the patient to a neck exploration for parathyroid tumor.

Another disease of childhood or adolescence that may cause confusion is Hand-Schüller-Christian's syndrome. If there is reasonable doubt a biopsy of an affected bone area may be necessary. However, the bone lesions in this condition are more often punched out, there is less tendency to expansion of the cortical shell, and skull involvement is much more frequent than in fibrous dysplasia.

Nonosteogenic fibroma is considered by some observers as representing not a specific disease entity but a variant of fibrous dysplasia. Hatcher and Schlumberger independently hold this view. It seems to be a difficult mat-

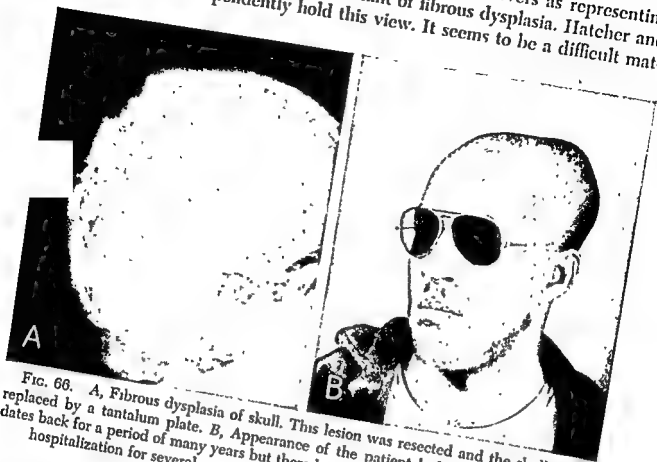


FIG. 66. A, Fibrous dysplasia of skull. This lesion was resected and the skull defect replaced by a tantalum plate. B, Appearance of the patient before operation. History dates back for a period of many years but there had been a recent skull trauma requiring hospitalization for several months. (Courtesy of McCloskey General Hospital.)

ter to separate the two conditions (if in truth they are unrelated) on purely histologic grounds although roentgenographic appearances are, in our opinion, sufficiently characteristic to make it possible to distinguish between them. In this connection it should be emphasized that the pathologist may find it impossible in certain instances to differentiate bone cyst from giant cell tumor and in others bone cyst from fibrous dysplasia. Yet we certainly do not admit that all three conditions are but variants of one another. The microscopic features of fibrous dysplasia are illustrated in Figures 70, 71, and 72.

TREATMENT

Sufficient experience has accumulated to make it appear that surgical treatment is justified for lesions that give rise to symptoms, that interfere with function, or that are increasing in size. If resection or wide excision is practical it is certainly the most satisfactory method. Curettage and implantation of bone material (chips or grafts) has yielded good results both in our hands and in the Army cases reported by Schlumberger.

If removal is incomplete, the same fibrous tissue may form again, healing may be retarded, and pain may persist. If there is marked deformity of a long bone, osteotomy may be fully justified in an attempt to correct it



FIG. 67. This case was amputated on the strength of a microscopic report of "fibrosarcoma"; roentgenographically it is entirely compatible with a subperiosteal giant cell tumor. Stewart considered it fibrous dysplasia on its histology. It well illustrates the difficulties that are encountered by the clinician. (Courtesy of Letterman General Hospital.)

Spontaneous fractures heal promptly. Even heavy radiation cannot be expected to eradicate a fibrous area in the center of a bone and it is conceivable that its effect on the physiology of adjacent normal bone may be unfavorable.

PROGNOSIS

The outlook in these cases is uncertain. Spontaneous restoration of the bone lesions to normal has not been observed. They may, however, reach a static state and in later years the activity of the pathologic process may diminish as far as one can judge from the microscopic appearance.

Stewart and the author, in 1945, recorded the first 2 cases of sarcoma

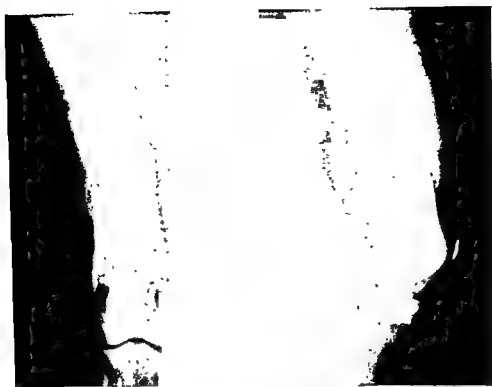


FIG. 68. Tumor which was regarded at the time of amputation fifteen years ago as osteogenic sarcoma both by roentgenographic and histologic study. In a recent review of the sections, however, Stewart considers the lesion to have been fibrous dysplasia. The clinical and roentgenographic evidences of a malignant tumor were quite definite.



FIG. 69. Fibrous dysplasia of femur associated with pathologic fracture in a soldier. Histologic confirmation (U. S. Signal Corps.)

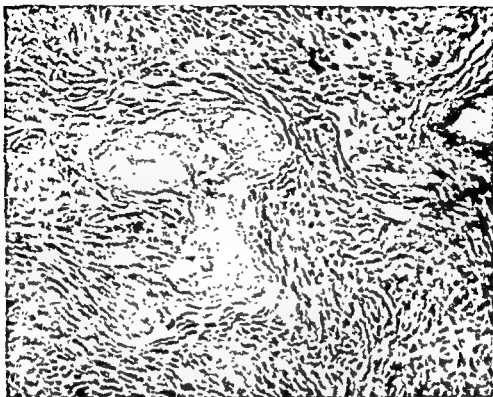


FIG. 70. Microphotograph of fibrous dysplasia of bone. Lesion made up of bundles of uniform-appearing spindle cells. In central portion there is a residual bone trabecula.

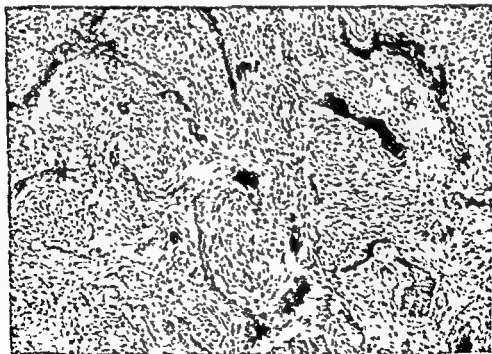


FIG. 71. Microphotograph of fibrous dysplasia. Note trabeculae of metaplastic bone developing in connective tissue.

developing on areas of fibrous dysplasia, and Jaffe has since reported a similar case and Stewart has seen another, as yet unreported. It is our opinion, therefore, that there is a definite likelihood such transformation may occur,

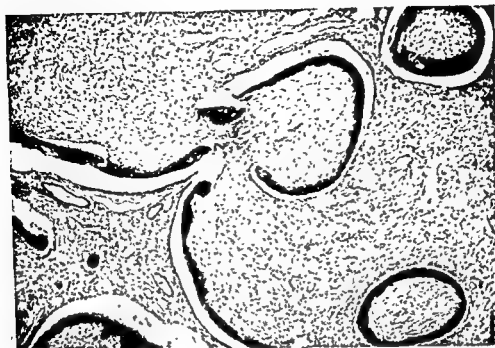


FIG. 72. Microphotograph of fibrous dysplasia. Curved spicules of bone developing at junction of loose edematous connective tissue. (Low-power magnification.)

and there is in all probability a long interval between the onset of the symptoms and the acquisition of malignant features. It would appear advisable to keep under careful observation all patients found to be suffering from fibrous dysplasia; any alteration in the clinical course or roentgenographic appearance should arouse suspicion of malignant changes.

The clinical records of the following 4 cases are of great interest and are given in some detail:

CASE REPORTS

Case 1

A Lithuanian female of 42, whose past history was uneventful, first complained of slight stiffness in her left shoulder five months prior to admission to Memorial Hospital. This increased in severity, pain developed which was worse on motion, and two months after the onset a swelling was noticed. A presumptive diagnosis of malignant bone tumor had been made at another hospital.

On admission the left scapula was the site of a large tumor, rounded, firm and non-tender (see Figs. 73 and 74). There were brownish pigmented areas involving the left anterior and posterior chestwalls, the entire left shoulder, and part of the neck. This distribution was essentially unilateral. There was pronounced limitation of movement of the left shoulder. Films of the left shoulder showed almost complete loss of outline of the scapula which was replaced by a very large

tumor mass, completely osteolytic, with only a few bony remnants remaining. The entire shaft of the left humerus showed altered architecture, with thinned cortex and multiloculated appearance of the medullary cavity. Films of the chest



FIG. 73. Osteogenic sarcoma of scapula arising on fibrous dysplasia.

showed marked deformity of most of the ribs, particularly on the left, with irregular expanded multiloculated areas. The lung fields appeared clear.

Films of the spine, pelvis, and femora taken a month later showed no changes in the spine, but the left ilium and the right pubis showed slight expansion and areas of decreased density similar to those seen elsewhere. Both femora showed widespread changes with decrease in density of the medullary cavities, which latter were irregularly expanded.

Lateral films of the skull showed a pagetoid appearance of the entire skull and facial bones with thickening of the tables and irregular areas of decreased density (see Fig. 75).

The scanty laboratory studies during this patient's first admission revealed nothing of significance unless a B.M.R. of plus 20 is indicative of some hyperthyroidism, since the latter has been emphasized in this disease. An aspiration biopsy was performed and yielded rare large atypical spindle cells, diagnostic of some type of sarcoma. Hence, a tentative diagnosis of medullary spindle cell sarcoma of bone was made.



FIG. 74. Same case as Fig. 73, showing typical pigmentation essentially unilateral in character. Late photograph after treatment by irradiation. In the shoulder area the pigmentary changes are partly the result of irradiation.

The tumor was not considered suitable for radical surgery since it was not realized at the time that the process in other areas was probably not sarcomatous, and the patient received a rather small amount of treatment with a radium



FIG. 75. Fibrous dysplasia. Pagetoid areas in skull and facial bones. An anteroposterior view revealed these to be mainly unilateral.

emanation pack. This totaled but 28,000 mg. hr. at 6 cm., and was administered on five successive days, from Nov. 19 to Nov. 23, 1929, through anterior and posterior portals. At the same time the patient received three roentgen-ray treatments to the left shoulder region, two over the rib areas, and two to the skull. The dose to the center of the tumor in the scapula was about 2100 r and the periphery received considerably less. Between Nov. 27, 1929, and Jan. 7, 1930, she received Coley's toxins both intramuscularly and intravenously with little reaction. Despite the seeming total inadequacy of the radiation, the patient's condition improved considerably. The tumor diminished in size, pain became much less severe and eventually vanished except for "slight pain with weather changes," as the patient described it.

Roentgenographic reexamination of the left shoulder on Dec. 24, 1929, showed a marked improvement in the appearance of the scapula with considerable decrease in size of the tumor and beginning calcification which suggested regeneration.

The patient was again able to conduct her housework in a normal fashion and

persistently refused to return to the clinic for observation. In fact, despite numerous appeals, she remained away for 11 years.

She reentered Memorial Hospital on July 9, 1941, and so far as the local findings were concerned the situation in the left shoulder was somewhat improved over that observed in 1929. Roentgenographs were reported as follows:

"Reexamination of the left shoulder on July 10, 1941, shows some residual soft-part tumor, but there has been marked regeneration of the scapula, with reformation of the glenoid and vertebral border. The humerus shows no significant change from previous status."

Films of the chest on the same date showed no apparent new changes in the ribs but there was increased density over the left chest, probably due to radiation. There was a large rounded shadow in the periphery of the right upper lung field which had the appearance of metastasis. The right humerus appeared normal. The pelvis showed no significant change. The skull again showed extensive changes which were better demonstrated and seen to be largely on the left.

The pigmentation was unchanged except for the addition of a large area of roentgen pigmentation, with scaling and telangiectasia. The patient's general condition had declined considerably. On this admission the laboratory studies were much more extensive. Red blood cells ranged from 2.5 to 2.9 million, except for a transient peak following transfusion. Calcium varied from 10.0 to 13.0 mg.; phosphorus from 2.82 to 4.11 mg.; alkaline phosphatase from 17.8 to 28.0 Bodansky units per 100 cc.; acid phosphatase was normal. Serum protein level on two determinations showed 7.8 and 8.1 per cent. Prothrombin level was 51 per cent. Chlorides ranged from 99 to 101 mg. per 100 cc. Chloride tolerance was abnormal and appeared suggestive of adrenal cortical insufficiency. Blood cholesterol studies showed total cholesterol 164 mg., free 56 mg., esters 108 mg. Bence-Jones studies were negative on several occasions. Two B.M.R. determinations were reported as plus 25 and plus 20.

Shortly after admission, but after a second aspiration biopsy, the patient developed a septic temperature ranging up to 103° F., and, since no cause could be otherwise elicited, it was assumed that the source was infected tumor tissue. On July 30, 1941, an open biopsy was made of the scapular tumor.

The tumor tissue was soft, friable, yellowish to grayish, in places very hemorrhagic. It was about the consistency of chicken-fat clot. On section it proved to be highly pleomorphic, nonbone-forming spindle and giant cell sarcoma. Giant cells reached enormous proportions and numerous atypical mitoses could be found. It was quite obvious that the tumor cells were identical with those obtained in the first material aspiration in 1929, and in the subsequent aspiration. This should be sufficient to dispel from the minds of those sceptical of aspiration as a diagnostic method any doubt that a malignant process existed in 1929. It does pose a difficult question as to why a large osteolytic malignant tumor had been present for so many years prior to dissemination.

Since it became desirable to prove in some other way than by roentgenogram that this lesion had arisen on a basis of polyostotic fibrous dysplasia it was determined in biopsy a supposedly nonneoplastic area for confirmation of this

diagnosis. Hence, on August 14, 1941, an 8.5 cm. portion of the left eighth rib was removed. On section this tissue showed no evidence of tumor and fulfilled all criteria for a microscopic diagnosis of fibrous dysplasia.

The patient was discharged August 28, 1941, clinically improved. Again she failed appointments, but this time probably because of progress of the tumor. Repeated attempts to persuade her to return to the hospital failed and she died at home on Dec. 2, 1941. During the terminal phase of the illness she complained of abdominal discomfort and diarrhea. Evidently the tumor on the left scapula had ulcerated and begun to fungate. A letter from her family physician stated that she had developed "intestinal" metastasis. Naturally, the authors were unable to confirm this finding in the absence of autopsy, but in view of the roentgenographic finding in the right chest they saw no reason to doubt the presence of abdominal disease.

Obviously this tumor ran a most unusual clinical course. It was diagnosed as malignant tumor of bone in 1929 on pathologic evidence, which we believe was entirely reliable. Under treatment, which should not have sufficed to control it, the patient experienced prolonged relief of symptoms, with regression and apparent quiescence of the tumor, and remained in relatively good condition over eleven years.

Case 2

G. deP. was an Italian male of 34, whose past history was uneventful except for a primary luetic lesion for which limited treatment had been given many years prior to admission. His present illness began nine months before admission when he noticed pain in the left lower thigh and leg. This became worse, and about six months later a swelling of the left hip was first noted. The swelling increased rapidly in size and was accompanied by severe pain.

On admission there was a bulky tumor mass involving the left hip laterally and posteriorly, and measuring 24 x 20 cm. in greatest dimensions. There was marked tenderness laterally over the greater trochanter. The bulk of the tumor was situated posteriorly and was of firm, rubbery consistence. There was limitation of motion of the left hip in all directions mainly because of pain. There was no increase of local heat.

Films taken at the time of admission revealed a pattern which is now considered classical for fibrous dysplasia. There were multiple, somewhat expanding areas of bone rarefaction, together with zones of increased density involving the left pubic bone, left femur, left tibia, and particularly the neck region (see Fig. 76).

On May 25, 1938, an aspiration biopsy was performed and a few cells were recovered which suggested malignant tumor. On May 31, the aspiration was repeated and a giant and spindle cell sarcoma, consistent with primary spindle cell sarcoma of bone, was diagnosed both on smear and sectioned fragments of clot. The resemblance to the previous case was striking.

Blood calcium ranged from 8.6 to 10.9 mg.; blood phosphorus from 2.6 to 4.09 mg. Phosphatase which ranged from 100 Bodansky units on admission to

24.9 on June 17, 1938, fell with treatment to 4.7 units on Nov. 8, 1939. B.M.R. was reported at plus 35, but for certain reasons this was considered inaccurate. The patient was treated by roentgen-rays, receiving a total of eighteen treat-



FIG. 76. Osteogenic sarcoma of femur developing on fibrous dysplasia. Note the separate area of involvement of tibia on the same side by fibrous dysplasia.

ments between June 1 and June 20, 1938. Portals were anterior, lateral, and posterior, approximately 15 x 18 cm. each. Daily doses were 300 r for a total of 1800 r per port, or a dose to the center of the tumor of 3130 r. The patient experienced a much more remarkable relief from pain than would be expected for the ordinary malignant bone tumor. Flexion and extension returned to a considerable extent. On Jan. 4, 1939, roentgenograms of the femur revealed considerable evidence of bone regeneration.

On March 8 the clinical improvement was regarded as so paradoxical that correctness of the diagnosis of osteogenic sarcoma was questioned. On November 8, 1939, the patient reported that he was essentially free from symptoms, and no tumor was palpable although diffuse thickening and firmness of muscles and subcutaneous tissues were noted. However, when referred for a check-up roentgenographic examination of the pelvis and left femur, he was found to have a

pathologic fracture in the region of the intertrochanteric line with considerable shortening of the femoral shaft and with coxa vara deformity. Approximately two months later further examinations showed no significant change. It appeared

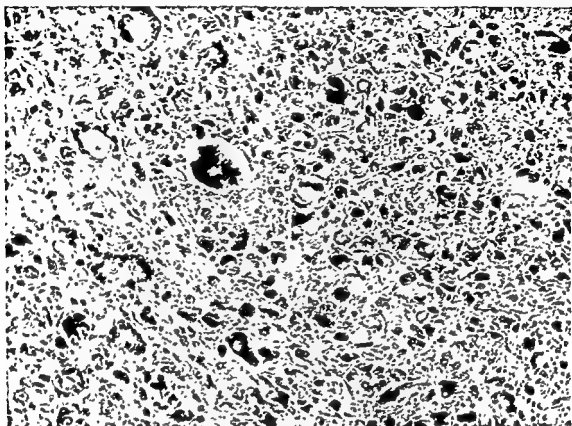


FIG. 77. Microphotograph showing pleomorphic large spindle and giant cell sarcoma arising in a case of fibrous dysplasia.

that a diagnosis of spindle cell sarcoma in an area of fibrous dysplasia was warranted, but to make more certain it was decided to obtain tissue from the involved area of the tibia and an open biopsy was performed on Feb. 8, 1940. This tissue was reported as fibrous dysplasia (see Fig. 77).

The patient returned to the Follow-up Clinic until July 15, 1942, and remained essentially symptom-free. In August, 1942, he entered another hospital complaining of epigastric pain and vomiting. His condition grew progressively worse and death occurred eight days after admission. No autopsy was obtained. Roentgenographs, however, are described as revealing an enlarged hilar shadow, with pulmonic infiltration, retraction of heart and trachea to the right, thickened pleura, and partial atelectasis of right lung. The roentgenologist's conclusion was: tumor of the left hilar region with metastasis to bone. Naturally, the evidence points entirely toward the left femur as a primary source of tumor. Again, in the absence of autopsy, one cannot be absolutely certain that metastasis had occurred, but with roentgenographic evidence pointing to metastasis and full knowledge that a malignant bone tumor existed doubt seems scarcely justified.

The type of malignant tumor which developed in these 2 cases of fibrous dysplasia was identical, namely, a pleomorphic spindle and giant cell sarcoma purely osteolytic. Both tumors showed a most unexpected favorable

response to radiation as compared with tumors of similar histologic appearance in different clinical settings.

Case 3

E.B., female, age 23 years, was first admitted to Memorial Hospital on Mar. 6, 1930, with the following history: Following a fall in childhood, asymmetry of the skull and face had developed and had been gradually progressive; six months prior to admission she noted pain and bulging of the ribs on the left side. Past history was noncontributory except that the patient began to menstruate at the age of 8½.

The physical examination disclosed a prominence of the bones of the left side of the calvarium in the temporofrontal region. The right malar eminence and zygomatic arch were also prominent. The right eye was noted to be about 0.5 cm. higher than the left. There was bulging in the region of the tenth and eleventh ribs on the left side. A tender mass 2 cm. in diameter was palpable to the right of the umbilicus.

Blood calcium was 12 mg. B.M.R. varied from plus 32 to minus 12. Roentgenograms of the skull and upper end of the femur revealed changes consistent with cystic osteitis fibrosa. She was given roentgen therapy to the right and left parathyroid regions; the ribs were treated with the radium element pack. In 1932 she developed scattered areas of pigmentation throughout the mucosa of both lips, cheeks, alveolar ridges, hard and soft palates, tip and lateral borders of the tongue; these increased somewhat thereafter.

In 1935 she delivered a baby which she nursed for an indefinite period. In 1937 there was some increase in the parietal and supraorbital prominence with exophthalmos of the right eye. Blood studies at that time were as follows: phosphatase 5.6 Bodansky units; phosphorus 3.56 and calcium 10.3 mg. For the next eight years she failed to return for a check-up but in January, 1945 she was admitted to New York Hospital. At this time the parathyroids were explored but no abnormal findings were observed. Ten days later a curettage of the femur was performed. Microscopic sections were reviewed and the diagnosis of fibrous dysplasia was established.

This is regarded as a typical example of Albright's syndrome (osteitis fibrosa cystica disseminata with pigmentation and sexual precocity)

Case 4

M.L., a 20-year-old Jewish male, was first seen at Memorial Hospital on May 17, 1944, with a history of onset of deafness in the right ear six years previously. At that time he was examined at another hospital and told that he had a tumor of the frontal bone. Roentgenograms were taken and a diagnosis of Paget's disease was made. In the following year the patient noticed that his right lower extremity had become shorter than the left, causing difficulty in walking. In 1943, a biopsy of the rib had been interpreted in another hospital as Paget's disease. A swelling in the left scapular region subsequently developed.

Physical examination on admission revealed a diffuse swelling in the right frontal bone measuring 10 cm. in diameter. There was also involvement of the

upper portion of the left clavicle. Blood studies at that time revealed: serum calcium 11.8 mg., phosphorus 2.78 mg., and alkaline phosphatase 19.3 Bodansky units. Roentgenograms disclosed a thickening of the calvarium and cystlike lesions involving the calvarium, mandible, sacrum, pelvis, right upper femur, and scapula. These findings were interpreted as polyostotic fibrous dysplasia. Because of the severe pain he was given roentgen therapy to the right hip with temporary relief. In January, 1946, following an unusual amount of activity, he noticed severe pain in the right leg. Films failed to reveal fracture. Shortly thereafter he was admitted to Memorial Hospital and a curettage and bone transplant was carried out. Microscopic sections were examined and reported as fibrous dysplasia. He was fitted with a brace and discharged on Mar. 16, 1946. When last seen in the Follow-up Clinic his condition was fairly satisfactory.

16. XANTHOMA OF BONE

THERE IS CONSIDERABLE DOUBT AS TO THE EXISTENCE OF A BENIGN TUMOR of bone which may properly be classed as a xanthoma. Only one case in our experience has been so designated by the pathologist. In this instance the lesion was a small localized area in the distal end of the radius, sub-cortical in position, purely osteolytic, and presenting some of the features of a nonosteogenic fibroma of bone. It yielded an excellent result to surgical removal (exposure and curettage).

We are inclined to the view that so-called xanthoma of bone is not a distinct clinical entity but represents lipid deposits in the tissues of some benign bone neoplasms, such as nonosteogenic fibroma, certain giant cell tumors of bone and monostotic fibrous dysplasia. This appears to be the opinion held by Schlumberger.

At all events one should bear in mind that when material obtained from a localized lytic area of bone which has the roentgenographic appearance of a small benign lesion is reported by the pathologist as a xanthoma, the treatment of such a lesion by adequate conservative surgery will yield satisfactory results. In other words, whether or not it is to be regarded as a distinct entity *sui generis*, it is benign and should be so treated.

17. GIANT CELL TUMOR (OSTEOCLASTOMA)

INTRODUCTION

THE TERM GIANT CELL TUMOR IS APPLIED TO A SPECIFIC VARIETY OF PRIMARY bone neoplasm with characteristic clinical features, roentgenographic appearance, and histologic picture.

Giant cell tumor occurs in the cancellous tissue at the ends of long bones, particularly the lower femur, upper tibia, lower radius, and upper fibula. It is essentially an osteolytic process which begins beneath the cortex and gradually extends to involve more and more of the bone until the shell of bone remaining may be entirely destroyed. Even when this occurs the periosteum remains as a limiting membrane. When extension to the articular cartilage takes place this too offers a considerable barrier to further progress, although at times the cartilage practically floats on a bed of tumor tissue. If weight-bearing is permitted, pathologic fracture may cause collapse of the involved portion of bone with resulting disturbance in the function of the joint. The tumor varies in its cellular composition; the character of the stroma cells determines the aggressiveness of the tumor which has wide individual variations. It is essentially a benign process and should be treated as such until it is established that malignant changes have taken place.

HISTORICAL

Cooper, in 1818, first described the benign nature of the giant cell tumor. Paget (1853) gave an outstanding description of it which remains as a classical contribution. Nélaton (1860) described the histologic and clinical features, and emphasized the fact that the process is only locally malignant (see Fig. 78). Two years later, however, Virchow suggested that it might recur and even prove malignant, alluding to the "degeneration into cancer" spoken of by writers since Paré. Gross, in America, analyzed 70 cases in detail and insisted on the benign nature of the lesion, although

admitting the difficulties in distinguishing it from malignant medullary sarcoma of aneurysmal type.

Before the advent of roentgenographic examination it was very difficult

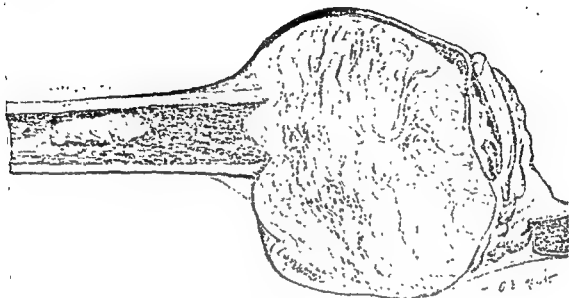


FIG. 78. "Myeloplaxic" (giant cell) tumor, upper end of tibia (A. Nélaton, 1889).

to make an early diagnosis and many giant cell tumor cases were subjected to amputation. Bloodgood and W. B. Coley independently advocated conservative treatment, warning against amputation as a needless sacrifice of limb. Bloodgood's insistence on the replacement of the term *giant cell sarcoma* by that of *giant cell tumor* did much to bring about a more conservative attitude toward the treatment of the disease.

Among the pathologists who have contributed to our knowledge of the histology of the lesion may be mentioned Ewing, Mallory, Goforth, Stewart (of Leeds), and Jaffe. Their investigations have established the histologic appraisal of individual cases on a much more firm prognostic foundation. It is certain that the cases encountered can be divided into fully benign, borderline, and malignant forms.

CLASSIFICATION

LOCATION

While giant cell tumors involving practically every bone in the body have been described, the long bones are principally affected. The femur, tibia, and radius account for at least 60 per cent of all cases. It is a solitary lesion. Rare reports of multiple lesions are probably instances of osteitis

fibrosa cystica generalisata with giant cell tumorlike tissue. However, we have seen both femora affected at different times and have on several occasions observed the condition extend across an articulation to involve the

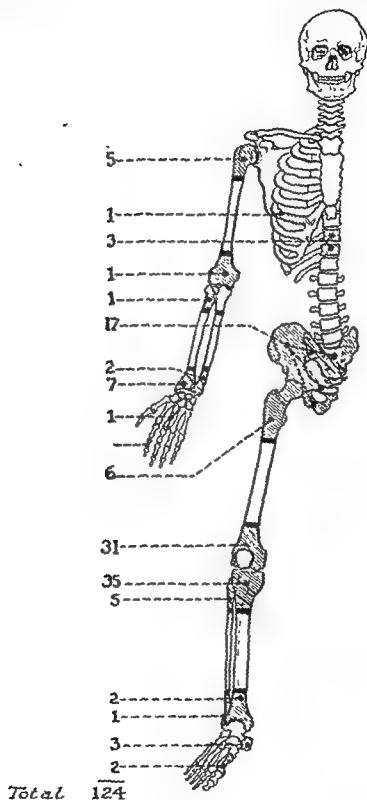


FIG. 79. Distribution of 124 cases of giant cell tumor.

other bone, e.g., tibia across to fibula, femur across hip to acetabulum. The patella is rarely involved, only about 14 cases being recorded. We have

encountered 1 benign and 1 malignant example. Similar lesions that may be found to involve the small bones of the hands and feet are usually of chondromatous nature (see Table XIII and Figs. 79-85).



FIG. 80. Giant cell tumor of thumb.

Giant cell tumor characteristically arises in the ends of long bones and progressively invades the cancellous portion. Only in late or neglected cases does it tend to extend appreciably into the cortical bone of the diaphysis. It is also unusual for this tumor to present itself as a marked eccentric

TABLE XIII
LOCATION OF GIANT CELL TUMORS

SITE	SERIES FROM MEMORIAL HOSPITAL AND HOSPITAL FOR THE RUPTURED AND CRIPPLED*			SCHURCH AND UEHLINGER'S SERIES COLLECTED FROM LITERATURE (385 CASES)		
	Cases	Proximal	Distal	Cases	Proximal	Distal
Femur	37	■	31	139	16	123
Tibia	37	35	2	106	92	14
Radius	■	1	7	65	3	62
Humerus	6	5	1	27	27	0
Ulna	2	0	2	29	7	22
Fibula	6	5	1	19	15	4
Ilium	7					
Sacrum	6					
Ischium	3					
Calcaneum	3					
Vertebra	3					
Metatarsal bones	2					
Metacarpal bones	1					
Phalanx	1					
Rib	1					
Pubis	1					

* Now the Hospital for Special Surgery

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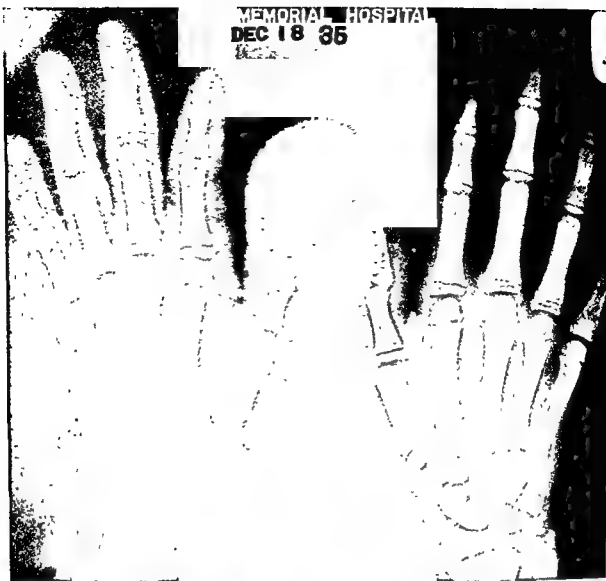


FIG. 81. Roentgenogram of case illustrated in Fig. 80.

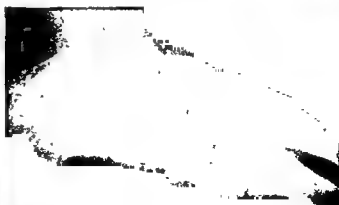


FIG. 82. A, Giant cell tumor. Note very rare location in cuneiform bone. B, Note in lateral view the bubble-like projection of tumor tissue with intact shell of bone. Compare with similar varieties of atypical giant cell tumor in Figs. 86-88.

swelling for it ordinarily destroys a considerable amount of the end of the bone before it produces much expansion. Hence, cases similar to those illustrated in Figures 86-92 are exceptional; when they are seen they are

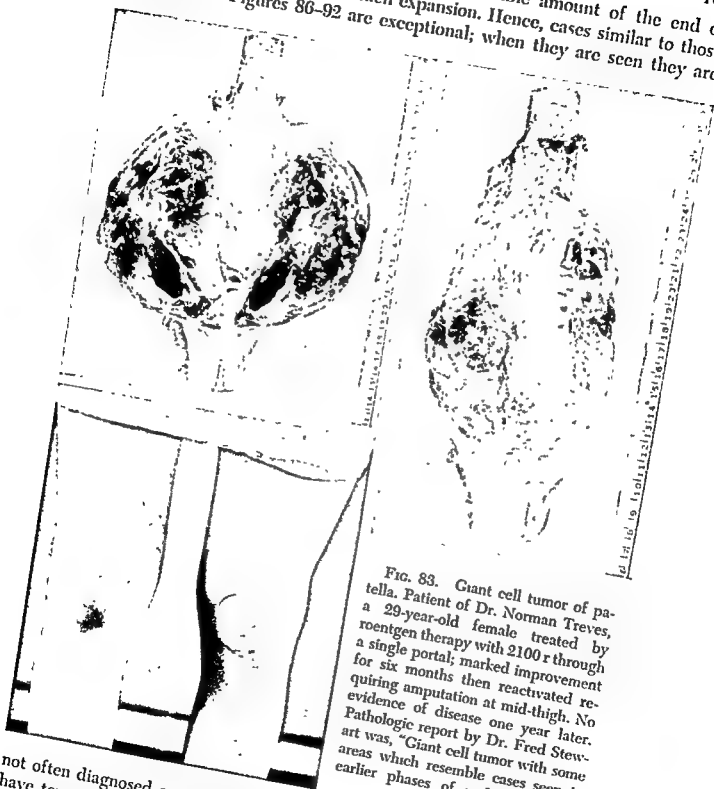


FIG. 83. Giant cell tumor of patella. Patient of Dr. Norman Treves, a 29-year-old female treated by roentgen therapy with 2100 r through a single portal; marked improvement for six months then reactivated requiring amputation at mid-thigh. No evidence of disease one year later. Pathologic report by Dr. Fred Stewart was, "Giant cell tumor with some areas which resemble cases seen in earlier phases of malignant transformation."

not often diagnosed correctly until tissue is examined microscopically. We have termed these cases *Subperiosteal giant cell tumors* because they extend more conspicuously beneath the periosteum to give rise to an eccentric tumor, in contrast to the usual centrally-placed variety. In our experi-

ence, results following surgical treatment in this atypical form of the disease have been more uniformly satisfactory than in those with greater bone destruction which were typically situated.



FIG. 84. Malignant giant cell tumor of the patella. In this case the growth was malignant from the onset and was treated by immediate total excision. The patient subsequently died of late pulmonary metastasis. Primary tumors of the patella are extremely rare.

Giant Cell Tumor of the Shaft

In rare instances subperiosteal giant cell tumors may arise at a distance from their customary location in the ends of long bones. In such cases the correct diagnosis is seldom made save by microscopic examination. The histologic appearance is indistinguishable from that found in giant cell tumor in its usual location. One must assume that the process is the same. However, these rare cases deserve a special classification as a rather distinct entity; we believe they are definitely related to the existence of a subperiosteal hematoma. All of the small group of cases we have studied have followed a specific direct injury of a severity calculated to produce such a periosteal hemorrhage. Schoolfield, in a personal communication, reports such a case in the shaft of the femur following a kick by a mule. In view of the greater likelihood of a malignant tumor occurring in the shaft, the diagnosis should be established by early operation and subsequent pathologic examination (see Figs. 90 and 91, p. 174).

In the case illustrated, Stewart considered it a benign giant cell tumor but was impressed with its telangiectatic character.

AGE

The fact is now well established that giant cell tumors are seldom encountered in patients younger than 20 years of age (see Table XIV). Le-

TABLE XIV
AGE INCIDENCE OF GIANT CELL TUMORS

PERIOD ^a (YEARS)	SERIES FROM MEMORIAL HOSPITAL AND HOSPITAL FOR THE RUPTURED AND CRIPPLED (124 CASES) ^b	COMBINED SERIES OF CHRISTENSEN (341), W. B. COLEY (50), AND BERING (26): TOTAL OF 417 CASES
0 to 10	1	23
11 to 20	21	106
21 to 30	48	150
31 to 40	30	63
41 to 50	16	49
51 to 60	6	19
61 to 70	2	7

^a Oldest patient, 88 years, youngest, 5 years, average age 29.7 years.

^b Now the Hospital for Special Surgery.

sions that resemble it in youth are either cysts or areas of fibrous dysplasia. The highest incidence is found in the period from 21 to 35 years. We have observed that giant cell tumors occurring in patients of 40 years or more tend to run a more aggressive course and to recur after surgical or radiation therapy.

SEX

We do not believe that sex is an important feature; there is little difference in the incidence in the sexes. This is borne out by the following study:

TABLE XV
SEX INCIDENCE OF GIANT CELL TUMORS

	SERIES FROM MEMORIAL HOSPITAL AND HOSPITAL FOR THE RUPTURED AND CRIPPLED ^a (124 CASES)		SERIES OF CHRISTENSEN (362 CASES)	
	Cases	Per Cent	Cases	Per Cent
Female	56	45	192	53
Male	68	55	170	47

^a Now the Hospital for Special Surgery.

ETIOLOGY

We know that the various theories of the etiology of tumors of bone in general have never been substantiated, and in this respect the giant cell tumor is no exception. Among the theories advanced are the following:

1. The *neoplastic* theory which assumes a true tumor arising in bone marrow.

2. The theory of *chronic inflammation* or *chronic irritation*, e.g., the faulty repair phenomenon (Mallory) or hemorrhagic osteomyelitis (Barrie).
3. The *traumatic* theory which assumes that injury induces a subcortical



FIG. 85. Giant cell tumor of sacrum. Result of irradiation. (Letterman General Hospital.)

hemorrhage in cancellous bone, the area involved gradually extending and progressively destroying adjacent bone. Codman was the strongest adherent of this theory and elaborated upon it as follows: "The essential structure of a giant cell tumor is simple, for it contains no walled blood vessels, and the corpuscles circulate through its interstices as if it were a sponge. Therefore, the whole sponge pulsates and tends to expand its bone walls by destroying its rigid boundaries. It does not advance down the soft marrow because the latter also pulsates with the same heart beats, nor

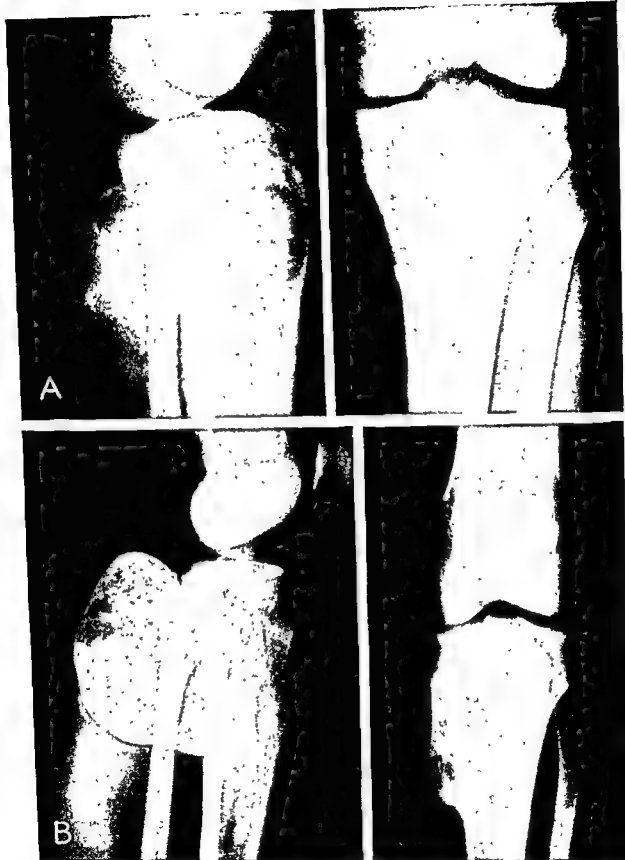


FIG 86. *A*, Atypical (subperiosteal) giant cell tumor. Note the balloon-like expansion projecting into the popliteal space. The anteroposterior view gives no indication of the subperiosteal nature of this lesion. *B*, End result of the treatment of this tumor by curettage. Chips of bone were not used, yet complete regeneration of the destroyed bone has taken place. Patient has been well with good function more than fifteen years.

does it invade joint cartilage, which is elastic and accustomed to the intermittent pressure of weight-bearing."

In further support of this theory, it should be mentioned that W. B. Coley, and Geschickter and Copeland noted a high incidence of trauma in the histories of their cases.

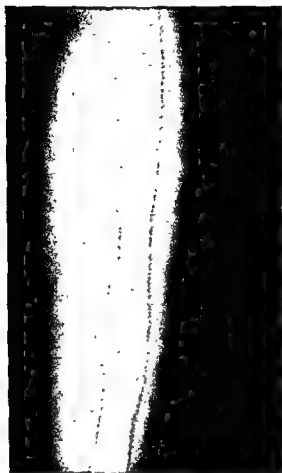


FIG. 87. Subperiosteal giant cell tumor in an atypical location. The diagnosis of Ewing's sarcoma was made prior to histologic examination. (Courtesy of Brooke General Hospital.)

CLINICAL FEATURES

As long ago as 1860 it was recognized by Nélaton that this disease is slowly growing (indolent) in its nature and may attain a considerable degree of involvement before the patient is



FIG. 88. Giant cell tumor in an unusual location (lesser trochanter). Note that the tumor is largely situated beyond the normal outline of the bone. (Courtesy of Brooke General Hospital.)

aware of its presence. It may require a mild trauma to call attention to the area affected even though it is then realized that a swelling has been present for a considerable time.

Pain is usually the first symptom. It is not of a degree or persistence comparable to that found in patients with the osteolytic form of osteogenic sarcoma with which it is at times readily confused. It is more a sense of mild discomfort generally made noticeable in lower extremity locations by exercise, walking, or prolonged standing. Upon complete rest of the part, the pain tends to disappear or to be so diminished as to attract little or no attention. At first its intermittent nature suggests the mild, dull ache often attributed by the patient to rheumatism. In its early phase, too, there may

be little or no swelling or other outward manifestation. In such cases there may be no limitation of range of motion in the contiguous joint. However, later, there is usually some restriction of the free range. In cases where

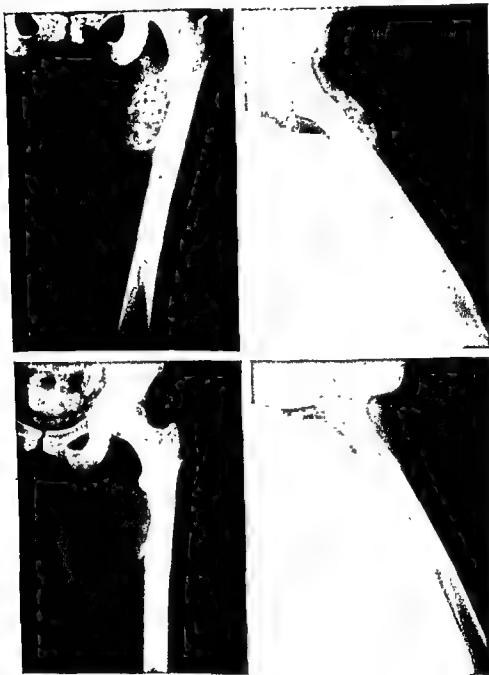


FIG. 89. Giant cell tumor atypical because of location. Preoperative roentgenograms above, postoperative below. (*Am. J. Roentgenol.* 47:544, 1942.)

expansion of the cortex has occurred slight swelling is often detected by either the patient or the examining physician.

In late cases, with marked destruction of bone and great expansion of the shell overlying the tumor, there is generally persistent pain which at times may be severe enough to require medication.



FIG. 90. Giant cell tumor in a most unusual location, the mid-portion of the femoral shaft. Diagnosis confirmed by open biopsy: A, Preoperative roentgenogram; B, roentgenogram after biopsy, C, roentgenogram following radiation therapy, D, roentgenogram three months after C. Note the ultimate healing of the area with excellent bone regeneration. Patient well eight years later.

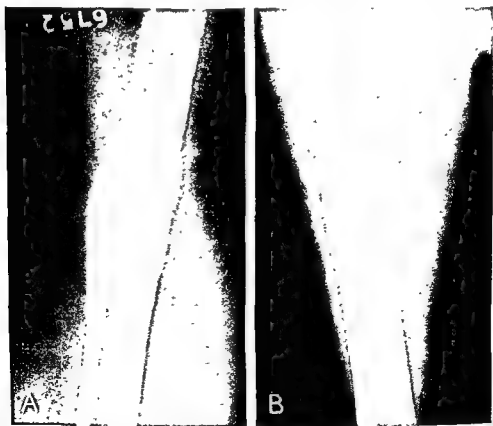


FIG. 91. A, Giant cell tumor of femoral shaft. When found in this atypical location the lesion is usually eccentrically placed B, Same case twenty-two years later. Treatment was surgical Compare with Fig. 90. (Case of Dr. Ben L. Schoolfield.)

The symptoms of a common complication, pathologic fracture, are indicative of the occurrence of a solution of the continuity of the bone; pain is sudden at the time of the fracture, the contour of the bone may be altered, and swelling is definitely increased. The occurrence of the fracture should be strongly suspected and roentgenographic check should be made at once.

Symptoms are often a reliable guide to the effect on the tumor of the surgical or roentgen treatment given. When, after either curettage or radiation therapy, a period of complete freedom from all symptoms is followed by the reappearance of pain or an increase of swelling there is a strong likelihood that a recurrence or renewed growth activity is taking place. Even after years of quiescence, the possibility of recurrence is always present upon the receipt of another injury to the affected part. Such a recurrence will be heralded by a return of pain.

Should pathologic fracture occur the symptom of disturbed joint function may be permanent, for such fractures in the tuberosities of the tibia or condyles of the femur produce an inequality of the joint surface similar to the "plateau" fractures seen in automobile or other serious accidents (see Fig. 93). In the latter, unless open operation accomplishes an anatomic reposition of fragments, such disability persists. The same is true for pathologic fractures in cases of giant cell tumor but with a more difficult problem involved in achieving anatomic realinement. In such cases persistent pain on walking or standing does not mean active tumor tissue is present; thus a fine distinction must be made between pain from active tumor and that from disturbed joint function due to poor alinement.

PHYSICAL SIGNS

Early in the course of the disease objective findings are notably lacking. Swelling is usually the first sign but may be inconspicuous. Disturbed joint function with inability to flex and extend within normal range is demonstrable. Pulsation of the tumor is rare even when the degree of destruction of the cortical shell is advanced.



FIG. 92. Benign giant cell tumor in an extremely early phase at which it was not possible to make an exact diagnosis on X-ray examination alone.

Palpation generally discloses an area of tenderness to deep pressure, though not differing from that encountered in cases of sprain of the adjacent joint; in cases involving the upper tibia, it may be suggestive of a



FIG. 93. Aggressive giant cell tumor. Note pathologic fracture. Cases of this sort must be regarded with suspicion and a guarded prognosis given.

derangement of an internal semilunar cartilage, a traumatized infrapatellar fat pad, or osteochondritis dissecans. Since so frequently the discovery of a giant cell tumor follows a definite injury, the examiner is prone to consider these intra-articular conditions as the cause of the symptoms. Such mistakes can be avoided if in all cases of knee injury with sustained symptoms early roentgenographic examination is insisted upon. The complete absence of objective physical findings, on the other hand, should not be an excuse for deferring roentgenographic study of the joint in which there is pain without obvious explanation, or which persists beyond the period when a trivial injury would have caused symptoms.

Effusion into the adjacent joint is not an early physical finding. Indeed, well established, extensive tumors may present little or no excess of joint fluid. When a marked effusion is seen, it indicates that the tumor has extended close to or has actually invaded bone adjacent to the reflection of the synovial membrane of the joint. Effusion is more often encountered in those cases of osteolytic osteogenic sarcoma which sometimes resemble aggressive benign giant cell tumor, or in synovioma.

ROENTGENOGRAPHIC FINDINGS

It has been asserted that this tumor presents such a clear-cut roentgenographic picture that the diagnosis could readily be made from the films

alone. It is true that the percentage of successful interpretations of this tumor is higher than for many other varieties of bone neoplasms, yet there are instances in which other lesions simulate the giant cell tumor so closely that some authorities decry the existence of a so-called typical or characteristic roentgenographic picture. Our experience has emphasized the folly of treating a patient with an unverified diagnosis of giant cell tumor. Too often has the "typical" lesion proven to be a malignant central sarcoma. Blind reliance on a film diagnosis is to be deprecated.

The usual roentgenographic features are a circumscribed osteolytic process occurring in the epiphyseal region of a long bone (see Fig. 94). It may also involve the adjacent metaphyseal region but usually does not extend far up the cortical bone of the shaft. Sometimes it may destroy both condyles, and most of the extremity of the bone may be invaded so that it extends to the articular cartilage; however, even late in the course of the disease the cartilage remains intact. Trabeculations may be seen which divide the tumor area into irregular compartments like the cut surface of an onion or like soap bubbles (see Fig. 95). Erosion sufficient to expand the cortex may destroy it so completely that no evidence of a bony shell remains (see Fig. 96). A pathologic fracture can be detected in the film although marked displacement is unusual. The fracture generally consists of a slight compression of the bone on the affected side so that tilting is seen with resulting unevenness of the joint surface.



FIG. 94. Benign giant cell tumor of femur. Note that at this stage the lesion is virtually confined to the lateral condyle.

PATHOLOGY

The gross pathology of this tumor, as described by Paget, Nélaton, and Gross, was concerned with advanced cases in which the lesions had attained great size and had often undergone necrosis, hemorrhage, and cystic softening. In modern times, because treatment is instituted earlier and amputations are seldom performed, pathologists have little opportunity of studying the entire gross specimen.

The region involved is a portion, or the greater part, of an epiphysis and the adjacent metaphysis. There is usually an asymmetrical involvement, extending from a subcortical position at one side of the epiphysis

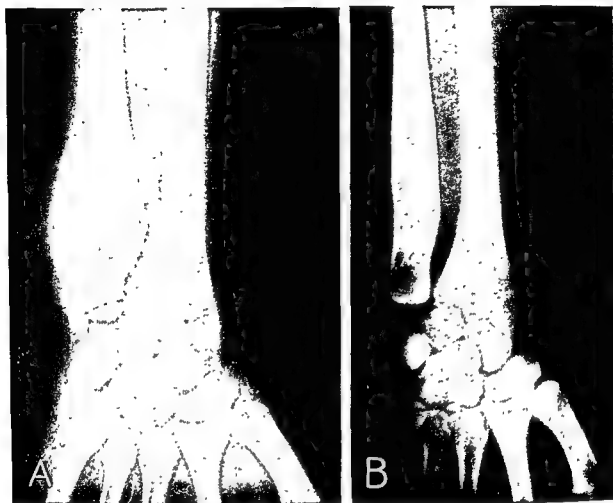


FIG. 95 A; Giant cell tumor of distal end of ulna. Note that the epiphyseal line is still evident. Such cases have been termed "giant cell variants of bone cyst." B, Appearance after curettage.

across the central portion by progressive destruction of cancellous bone. There is usually an expansion of the bony shell about the tumor so that it becomes thin and in places may even be entirely absent (see Fig. 97). In the early stages there may be trabeculae traversing the tumor irregularly but as growth continues these may be largely resorbed. Even when the shell of bone has almost disappeared the periosteum tends to establish a limiting membrane which prevents actual extension into the soft parts. There is little, if any, periosteal reaction and no tendency in untreated cases toward the development of reparative bone within the tumor-bearing area.

The tumor tissue itself is markedly hemorrhagic, friable, and its appearance has been likened to currant jelly. It may show all shades of color from red to black; some are pale, almost white, or putty-colored. At operation it



c. 96. Benign giant cell tumor, telangiectatic type. Roentgenographic diagnosis was osteogenic sarcoma (osteolytic type).



FIG. 97. Giant cell tumor, aggressive form. Note the striking progress the tumor has made in a three-months' period during which no treatment was carried out. In the first view the lesion is susceptible of curettage, in the second view its operability is very doubtful, and it is questionable whether it would yield a favorable response to X-ray therapy (Patient a German prisoner of war, Glennan General Hospital.)

shows a marked tendency to bleed, oozing taking place as from a sponge. Fibrous septa often course through the tumor-bearing area, and in some of these spicules of bone persist. Both at the margins of the epiphysis and in the cortical area of the adjacent shaft the progress of the destructive process is retarded by dense cortical bone. This results in extension of the disease across the epiphysis to the opposite side before much progress is made either up the shaft or in destroying the shell of cortex at the site of origin. The invasion is usually halted at the joint cartilage which offers a real barrier to further extension in this direction.

The wide destruction of bone renders these cases liable to pathologic fracture and this complication may then alter the subsequent course of the tumor growth.

MICROSCOPIC APPEARANCE

The tumor consists essentially of a stroma of round cells and spindle cells in which are interspersed multinucleated giant cells. The latter may be present to the number of from 20 to 35 per low-power field and their nuclei vary in number up to more than 100 in each cell. The cells may vary in size from 10 to 100 microns, but from 30 to 60 is the average. There is wide variation in the number of giant cells per field in individual tumors or in different areas in the same tumor. However, the cells themselves retain a marked regularity as regards the multinucleated elements. Where cells are found with few nuclei small and sparsely scattered through the cell, one should suspect that they may represent a malignant type of giant cell and that the tumor is a true sarcoma rather than a benign giant cell tumor.

From a prognostic viewpoint, the important feature is the stroma cell. These are mononuclear and look like young connective tissue cells. They may appear round, ovoid, or spindle in shape. The nucleus occupies much of the cell; the chromatin is moderate; the nucleolus is centrally placed. Collagenous intercellular material is abundant in inverse ratio to the compactness of the stroma cells.

The grading of giant cell tumors has recently been attempted by Jaffe. He believes that while they fall readily into three groups there are some, especially the recurrent, infected, or heavily radiated tumors, that are difficult of assignment. This seems a worthwhile endeavor; indeed, abortive efforts in this direction have been made by earlier investigators.

In a personal communication Jaffe has explained his grouping of giant cell tumors as follows:

Like the gross, the histologic picture of giant cell tumor is clearly characterized. The viable and otherwise unmodified tumor tissue is composed essentially of a vascularized network of spindle-shaped or ovoid stromal cells, heavily interspersed with multinuclear giant cells [see Fig. 98]. Mainly on the basis of

differences in stromal-cell detail, one can grade the giant cell tumors in respect to their aggressiveness [see Figs. 99 and 100]. Aggressiveness is attested by increase and crowding of the stromal cells, plumping up of these cells, and

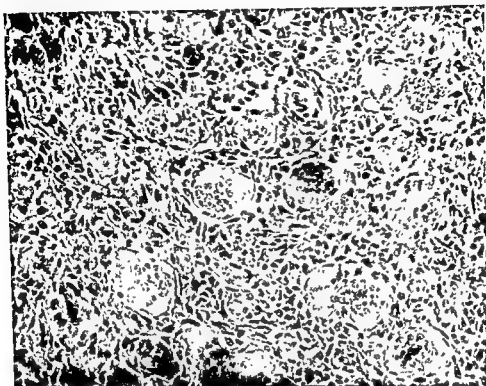


FIG. 98. Microphotograph of giant cell tumor. Note numerous epulis giant cells in orderly spindle and oval-cell matrix. Delicate capillary network of blood vessels.

particularly of their nuclei, the presence of many stromal cells undergoing mitotic division, and the presence of stromal cells with one or more very large nuclei. Along these lines, we subclassify giant cell tumor into three grades—I, II, and III—showing respectively, no appreciable, moderate, and pronounced atypism of the stromal cells. The giant cell tumors of grade III present a sarcomatous stroma and are already frankly malignant. Occasionally a malignant giant cell tumor is already so (that is, a tumor of grade III) when studied for the first time anatomically. Usually, however, grade III represents malignant transformation, through successive recurrences, of a tumor which, when first studied, was of grade I or II. The prognosis in cases of malignant giant cell tumor is very bad, because of its strong tendency to metastasize [see Fig. 101]. Indeed, very often the tumors of grade II already show such local clinical aggressiveness that the affected limb has to be amputated.

DIFFERENTIAL DIAGNOSIS

Codman has stated that there are three possibilities of error in making a diagnosis of giant cell tumor from roentgenograms, and two from microscopic sections:

1. The films may be characteristic and yet the sections may be unequivocally in favor of some other diagnosis.

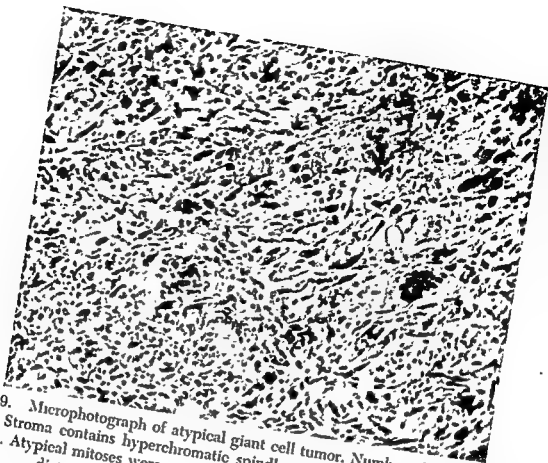


FIG 99. Microphotograph of atypical giant cell tumor. Number of epulis giant cells reduced. Stroma contains hyperchromatic spindle and irregular-shaped cells, many of large size. Atypical mitoses were not found in this tumor but would regard as intermediate state in development of malignant giant cell tumor.

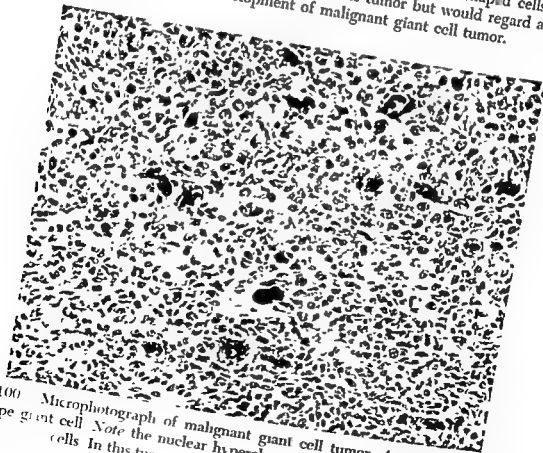


FIG 100. Microphotograph of malignant giant cell tumor. An occasional residual epulis-type giant cell. Note the nuclear hyperchromatism and pleomorphism of stromal cells. In this tumor atypical mitotic forms were present.

2. Both films and sections may be interpreted as giant cell tumor and yet the rapid fatal course may indicate an error of interpretation.
3. The films, sections and clinical course for several years may seem to

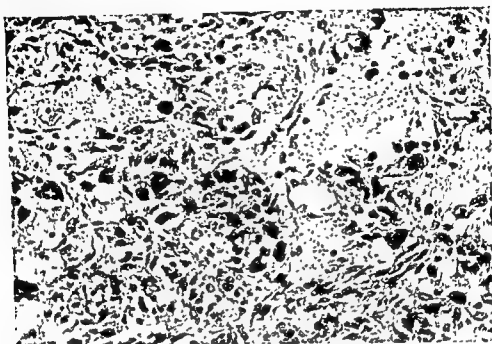


FIG. 101. Microphotograph of malignant giant cell tumor presenting a distinct angioblastic pattern.

assure the diagnosis and yet a sarcoma may eventually appear at the site of the lesion.

There are many bone lesions to be distinguished from the giant cell tumor; some are malignant, some are benign, and some are not neoplasms at all. Table VII (p. 45) presents the distinguishing factors, and shows that age and consequent relationship to the epiphyseal line are the most important elements to be considered in trying to differentiate them.

Bone Cyst

The following features of bone cyst should distinguish this condition from giant cell tumor: The age of the patient with bone cyst is generally below that at which the epiphysis closes in contrast to giant cell tumor in which the epiphysis of the involved bone has usually already closed. The site of the lesion in bone cyst is on the diaphyseal side of the epiphyseal line while in giant cell tumor it tends to arise in cancellous bone on the articular side of the already closed epiphyseal line.

The symptoms of bone cyst are mild, or even absent, and in one-half of the cases the condition is not recognized until a pathologic fracture has been sustained. The process tends to extend more gradually in cases of bone cyst than it does in giant cell tumor, yet this condition is most often confused with giant cell tumor. They have many features in common. The

NEOPLASMS OF BONE

microscopic appearance may be quite similar. Sabrazes, Jeanneney, and Mathey-Cornat, in their introductory remarks on giant cell tumor, bone cyst, and fibrous osteitis, point out that the nature of these three conditions is not well understood, and that transitional forms may be found. They prefer to retain them under the classification of *tumors* rather than *lésions dystrophiques des os* as Lecène and others have designated them, although recognizing that their prognosis is infinitely better than that of true malignant tumors.

Benign Chondroblastoma (Codman's epiphyseal chondromatous giant cell tumor)

Situated in the same portion of the bone as giant cell tumor and resembling it superficially on roentgenograms, this relatively uncommon lesion generally occurs in younger patients prior to epiphyseal closure, is less aggressive, and is characterized by areas of calcification which give it a mottled appearance not seen in untreated giant cell tumors. Histologically the distinction is not difficult (see Chap. 11, p. 112).

Hyperparathyroidism (Recklinghausen's disease)

This disease (multiple form of osteitis fibrosa cystica) seldom offers diagnostic difficulty because the lesions are multiple and involve the shaft; in fact, except for the microscopic picture, it bears no similarity to giant cell tumor. The blood chemistry is important, for in bone cyst and giant cell tumor the serum calcium, phosphorus, and phosphatase are normal whereas in Recklinghausen's disease the serum calcium and phosphatase are increased and the phosphorus is diminished.

Central Chondroma (Chondromyxoma)

This condition, when occurring in the epiphysis of a long bone, occasionally simulates a giant cell tumor; the roentgenograms may even be indistinguishable. Since conservative treatment is in order for each, the diagnosis will ultimately rest on the microscopic evidence obtained either by aspiration or at operation.

Plasma-Cell Myeloma

This disease affects individuals who have passed the age period when giant cell tumor is ordinarily found, yet there is a slight overlapping about the age of 40. In this small group the solitary form of myeloma, especially when occurring in flat bones such as the ilium, may require histologic study for differentiation.

Osteogenic Sarcoma

The consideration of this type of bone tumor will be restricted to the form called the *medullary osteolytic* variety. This tumor often selects the

same site in bone, occurs in the same age group, has in its earlier stages a similarity of symptoms and signs, and even resembles the giant cell tumor roentgenographically. We have encountered a number of cases that had been regarded as giant cell tumors and treated by radiation over a long period only to require amputation when it had become obvious that the lesions were malignant osteolytic sarcoma and not benign giant cell tumor. *This may happen whenever a supposed giant cell tumor is treated by radiation without microscopic confirmation of the diagnosis.*

TREATMENT

There is still no general agreement as to whether this tumor should be treated by means of radiation (roentgen-rays) or surgical methods (resection or curettage). Such radical measures as amputation have been properly discarded as a primary method of therapy, being reserved only for established cases of malignant giant cell tumor or for the exceptional case occurring in the lower extremity in which earlier conservative measures have yielded such an unsatisfactory functional result that the substitution of an artificial limb seems advisable.

As to the advantage of the two methods—radiation and surgery—it is interesting to note that there are extremists on both sides. Some would use surgery regardless of the size, location, or extension of the process; others would never resort to surgery but would treat all by roentgen-rays. Such a divergence of opinion would indicate that neither extreme view is correct and that the profession should retain an open mind until a more satisfactory answer has been found.

If the opinions of the majority of surgeons and radiologists are considered it will be found that radiation is regarded as preferable for tumors in inaccessible regions and surgery for accessible ones (see Fig. 102). An exception, however, is the neglected, advanced tumor in which encroachment of the joint and complete destruction of the bony shell have resulted. These cases are not generally acceptable for curettage. If the involved bone is the fibula or ulna and a resection can be performed without too great sacrifice of function, this measure should be carried out. If the involved bone is the femur or tibia, radiation is the better method and has yielded some favorable results.

TREATMENT BY RADIATION

Some of the arguments advanced by those who favor radiation for operable cases may be briefly considered.

Cutler, Buschke, and Cantril have made perhaps the most unfavorable comparison of surgery to radiation in the treatment of giant cell tumor. They state that surgery results in impaired joint function and is associated with a recurrence rate of 25 to 30 per cent. Radiation, on the other hand,

they prefer because it respects the capsule of the tumor, eliminates the danger of infection, has less unfavorable effect on function, possesses at least as high a cure rate as surgery, entails no more prolonged period of

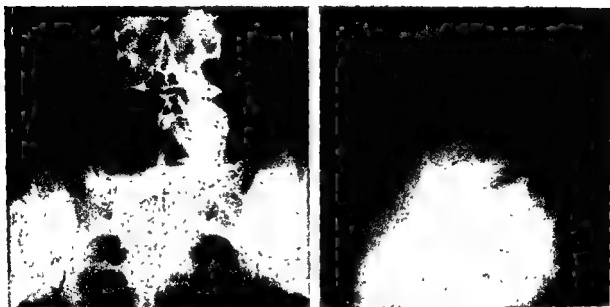


FIG. 102. Giant cell tumor of the fifth lumbar vertebra.



FIG. 103. A, Extensive giant cell tumor of upper femur with complete loss of the outline of the head and neck of the bone and extension across to the acetabulum. B, Appearance following prolonged heavy radiation. Note bone regeneration in the acetabular as well as the upper femoral region. Solid bony union took place between these two areas and the patient was able to walk despite four inches of shortening. He resumed his former occupation and lived seventeen years, but died of pulmonary metastases.

disability than does surgery, and accomplishes a cure in almost all patients when adequate dosage is used.

Our experience leads us to state that this view is highly misleading

and at variance with that of most investigators in this field. It is certain that fewer cases of giant cell tumor in accessible locations are being treated by radiation than was the case fifteen or twenty years ago. It is also our

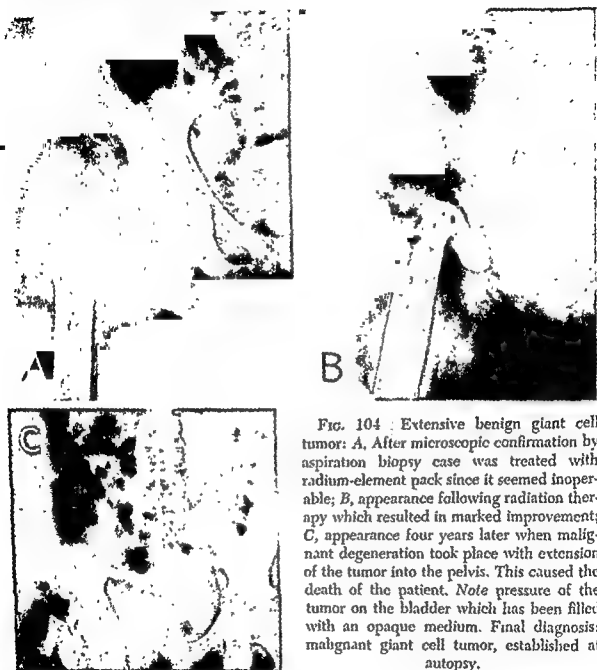


FIG. 104 : Extensive benign giant cell tumor: A, After microscopic confirmation by aspiration biopsy case was treated with radium-element pack since it seemed inoperable; B, appearance following radiation therapy which resulted in marked improvement; C, appearance four years later when malignant degeneration took place with extension of the tumor into the pelvis. This caused the death of the patient. Note pressure of the tumor on the bladder which has been filled with an opaque medium. Final diagnosis: malignant giant cell tumor, established at autopsy.

opinion that the profession in general is seldom made aware of the failures of roentgen therapy or of the late unfavorable sequelae (see Figs. 103 and 104).

Geschickter states that "where a weight-bearing limb is involved the probability of restoring function is doubtful." However, he prefers surgery for patients in middle life and in whom function is vital to their occupation and livelihood. He believes that "irradiation is far slower in its effects and disables the patient for too long a time."

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According to Bloodgood, "the greatest danger from irradiation is to persist in it too long, especially if the bone lesion is resectable."

Phemister and W. B. Coley each pointed out the unfavorable results that might follow radiation; the latter stressed the greater danger of pathologic fracture developing after radiation.

It should be explained that the appalling results of over-irradiation occurred when the method was in its infancy; they can be directly charged to excessive dosage. Radiologists are now more conservative and over-treatment is much less frequently encountered.

Jansson presented a report of ten- to twelve-year cures in 4 cases of giant cell tumor treated by roentgen radiation only. The lesions were located in the lower end of the femur or the radius. The patients were between the ages of 20 and 33 years. He states that low dosage of roentgen rays (500 to 1000 r) given every second month until distinct ossification appears (three to four months) provides adequate treatment. He notes that after irradiation an initial period of increasing osteoclasia occurs before healing begins. One patient was cured by one dose of 600 r. In the past, bad results (dermatitis and ulcers) have been due to heavy dosage for this benign tumor. He expresses the opinion that the tumor recurs less frequently after irradiation than after curettage.

Hilton reports 3 cases of giant cell tumor in which healing and recalcification occurred after roentgen therapy. Follow-up information was received from 1 patient for seven years and from another for eleven years. In 2 cases a diagnosis of sarcoma had been made elsewhere prior to treatment. Periosteal lifting and absorption of a large part of the cortex were evident on roentgenographic examination. The first evidence of healing after roentgen therapy was the reappearance or increase of the trabeculae. Hilton agrees with Jansson that the osteolytic type of giant cell tumor is only a more advanced form of the trabeculated type. After irradiation, in the initial period, the tumor temporarily grows larger and more osteolytic and the bone is prone to fracture. This is followed by a period of healing. This author favors irradiation rather than surgical treatment of osteoclastomas. It is still a fact that there is no generally accepted standard of technique for the irradiation of giant cell tumors. This is due, perhaps, to the wide variation in dosage required to bring about the desired result. A dose which in one case is followed by regression of the tumor and ultimate regeneration of bone in the involved area will in another apparently similar case be found to be entirely inadequate.

It would seem indisputable that before beginning radiation therapy of a suspected giant cell tumor one should be assured of the correctness of the diagnosis. Many cases treated on a roentgenographic diagnosis alone have later proven to be malignant central sarcoma for which amputation would have been the proper method of treatment. Such a mistake in diag-

nosis is highly undesirable as is the removal of a bit of tissue by an open (surgical) biopsy. Cases handled in this manner often do not respond well to subsequent radiation. Occasionally they are accompanied by sufficient hemorrhage to induce the operator to pack the wound. An aspiration biopsy, if successful, obviates the necessity for an open biopsy and yet yields a diagnosis which permits of radiation therapy without the hazard of mistreating a central sarcoma.

COMBINATION OF RADIIUM AND SURGERY

As might be expected, earlier workers have tried various methods of radiation and surgery. The use of radon introduced into the cavity after curettage was a method that was followed by the most disastrous results. Its dangers have been exposed by many authorities, and the method has been entirely abandoned. Failure of wound healing, infection in devitalized bone sometimes spreading to the neighboring joint, fungation of the tumor, and malignant transformation have all followed the use of radon inserted in the curetted cavity of a giant cell tumor. There is no excuse whatever for combining curettage and radium treatment in this manner.

PREOPERATIVE ROENTGEN THERAPY

It is not advisable to give preoperative roentgen therapy as a deliberate, planned procedure, for if surgical methods are to be employed there is little to be gained by preceding it with radiation, and where radiation in considerable dosage (1200-1500 r to each portal) has been given there is apt to be interference with subsequent wound healing and bone regeneration. In such cases it is better to rely solely on radiation (see Fig. 105). However, if before the patient is seen he has already received mild doses of radiation administered in a single course, there is little risk of proceeding with curettage.

The method of choice is surgery without preliminary radiation.

POSTOPERATIVE RADIATION

Although some surgeons administer small doses of roentgen therapy after operation, the consensus of opinion is against such practice. There is admittedly less danger from postoperative than from preoperative therapy for once the wound is healed there is slight risk of wound complication. Possibly small doses are not harmful; the advantages, however, are not clear.

TECHNIC OF RADIATION THERAPY

Formerly institutions possessing large amounts of radium used radium emanation or the radium-element pack in the treatment of giant cell tumors. More recently, however, this agent has been practically supplanted by high-voltage roentgen-rays. The latter is available in most localities, is

much more economical, and requires a far shorter period of time in which to deliver a comparable dose.

While 200-kv. therapy is widely used, there are experienced roentgen-



FIG. 105. Giant cell tumor of lower femur treated by curettage and packing, later roentgen therapy. Pathologic fracture and recurrence. Amputation. Patient lived without evidence of recurrence or metastasis for ten years. Died following hysterectomy in another institution.

ologists who favor a lower voltage, that is, 125–150 kv. for giant cell tumors in relatively superficial positions, such as the radius, femur, tibia, and fibula. With this voltage, a 4-mm. aluminum filtration at 25–30 cm. TSD is used. In this manner a threshold erythema dose of approximately 500 r (depending on the size of the portal) is given at a single treatment. The number of

portals varies with the location of the tumor, but 2 is the usual number for tumors located in the extremities. Each portal is treated at an interval of from four to seven days. A cycle consists of four such treatments, two to each portal. Where higher voltages (200-250 kv.) are used the factors are modified. Usually the dose per treatment is lowered and the number of treatments increased.

Following the completion of a course of therapy it is often noted that the tumor-bearing area tends to swell and sometimes the patient is aware of increased discomfort. Formerly roentgenologists often interpreted these symptoms as indicating an increase in growth activity of the tumor, and gave larger doses in the next cycle which was administered soon after the initial one; thus it often happened that the dosage delivered was much in excess of what is now recognized as a safe maximum. Not infrequently the ultimate results were skin and soft-part damage, radiation osteitis, failure of bone regeneration, and ultimate loss of the limb.

Since roentgenologists in general now appreciate the hazards of excessive doses, these untoward complications are far less frequent at the present time, yet there is still no well-established plan of treatment that has been generally accepted. We have noticed that tumors apparently quite similar in size and location respond quite differently to the same dosage and factors. In large doses the regenerative powers of bone are inhibited or destroyed and in small doses arrest of the tumor is not usually accomplished. These, it appears, are distinct disadvantages of the radiation method of treating giant cell tumors.

The importance of the principle of adequate support during the period of bone repair is as vital during and after radiation therapy as it is in cases treated surgically. This period is longer in radiated than in operated cases. Neglected limb support results in pathologic fracture with almost certain impairment of the final functional result and unfavorable alteration in the course of the disease.

When a case of suspected giant cell tumor has been subjected to aspiration biopsy, the diagnosis thereby confirmed, and treatment by X-ray therapy instituted, most careful observation is necessary. This should consist of clinical as well as roentgenographic reexamination at regular and not too infrequent intervals.

Following the administration of a dosage that has been decided upon as adequate, if symptoms become progressive and if evidence of continued destruction of bone is present, the temptation exists to add further courses of roentgen therapy. Often, however, these additional treatments are not followed either by symptomatic relief, cessation of bone destruction, or commencement of the healing phase. At this point there is uncertainty as to future procedure. Shall the roentgenologist persist with even more therapy or shall the surgeon now attempt to ablate the cavity by curettage?

In all probability neither of these procedures will produce a satisfactory result; curettage is definitely contraindicated after heavy radiation therapy.

In such cases there is always the possibility that malignant transforma-

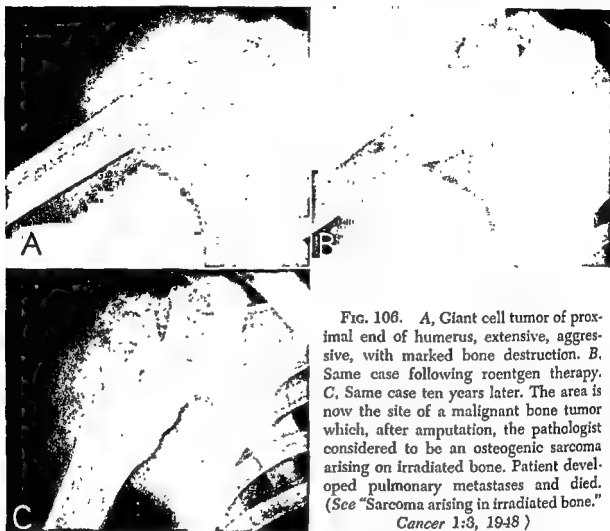


FIG. 106. A, Giant cell tumor of proximal end of humerus, extensive, aggressive, with marked bone destruction. B, Same case following roentgen therapy. C, Same case ten years later. The area is now the site of a malignant bone tumor which, after amputation, the pathologist considered to be an osteogenic sarcoma arising on irradiated bone. Patient developed pulmonary metastases and died. (See "Sarcoma arising in irradiated bone." *Cancer* 1:3, 1948)

tion of the previously benign tumor is taking place. This has happened often enough in our experience to make us exceedingly sceptical of the eventual outcome (see Fig. 106). The safest course is to perform further aspiration biopsy which may determine the fact of such malignant alteration and thus indicate the necessity for immediate amputation. If skilled interpretation of the material obtained by aspiration biopsy is not available, there may be circumstances where open biopsy might be considered, followed by layer closure of the wound. This procedure, in a case already heavily radiated, is by no means without hazard and cannot generally be recommended. Thus the surgeon and the roentgenologist are in a quandary and there is no certain way to avoid it.

On the one hand, to amputate without absolute confirmation by microscope of the suspected malignant nature of the tumor is to run an unjustifiable risk of performing an unnecessary mutilating operation, yet on the

other, to delay until there is not the slightest doubt of its malignant qualities is to postpone amputation until it is too late to save the life of the patient.

There are few situations in the entire field of bone tumors which afford greater anxiety or which tax the judgment and intuition of the professional adviser more sorely than these cases of giant cell tumor which fail to yield to radiation therapy. While they are the exception rather than the rule, they occur with sufficient frequency as to constitute a real problem. It is for this, as well as for other reasons already mentioned, that surgical treatment from the outset is preferred for giant cell tumors in accessible locations.

SURGICAL TREATMENT

Generally speaking, giant cell tumors occurring in bones inaccessible to surgical approach should be treated by irradiation. Tumors of the ulna and fibula, if rather extensive, are amenable to resection without great sacrifice of function and with the assurance of a successful end-result. Tumors of the upper end of the femur are not always easily accessible to curettage and the operation may be quite difficult; irradiation may therefore have to be employed in this location. Tumors occurring in the lower femur and the upper tibia seem to us to be particularly adapted to curettage. They are accessible, the functional result is excellent, the period of disability is shortened with obvious economic advantages, and furthermore, a pathologic fracture is avoided. We find that pathologic fracture has complicated approximately one-fourth of our giant cell tumors of the long bones treated by irradiation. This high incidence doubtless could be lowered by greater restriction of activity and more careful splinting and protection during the prolonged period often necessary for bone regeneration following

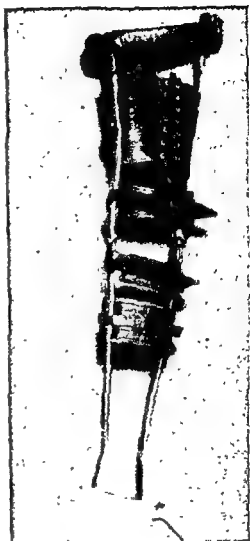


FIG. 107. Walking caliper splint with movable knee. This is a most useful method of preventing weight-bearing in cases of bone cyst and giant cell tumor. It also serves to prevent pathologic fracture in other types of bone tumor undergoing conservative treatment, such as metastatic carcinoma, plasma cell myeloma, and so forth.

roentgen-ray therapy (see Fig. 107). It has been our experience that where pathologic fracture has occurred, joint function usually suffers permanent impairment.



FIG. 108. Giant cell tumor before and after curettage. No bone chips were used.

CURETTAGE

For most giant cell tumors which are not suitable for resection the operation of choice is curettage. This procedure is applicable to tumors of the distal femur, proximal tibia, distal radius, and proximal humerus, and to the majority of those in other sites (see Fig. 108).

The necessity for thoroughness in removing tumor tissue makes attention to technical details of the procedure a matter of first importance (see Chap. 49, p. 486). Wound closure is imperative (see Fig. 109).

RESECTION

This conservative surgical measure is adapted for lesions in nonessential bones, i.e., those in which the removal of a considerable segment of bone does not leave a useless limb or necessitate an amputation. An example is resection of the upper portion of the fibula for giant cell tumor, or of the rib or metatarsal for the same condition. It has long been recognized that a complete resection of the disease-bearing portion of the shaft of the bone is not followed by recurrence of the disease. Therefore, it is a procedure to be considered seriously in contradistinction to curettage in loca-

tions where it is suitable. Also, it is useful in those cases in which the disease has recurred after curettage.

For giant cell tumor of rib, subperiosteal resection is the ideal procedure



FIG. 109. Giant cell tumor of tibia. Fungation of tumor tissue following failure to close the wound after curettage. This error was responsible in large measure for the unfavorable results of surgery which were not uncommon some years ago.

It is unnecessary to excise more than a few centimeters of the adjacent bone.

Subperiosteal Resection of Tumor-bearing Area

In 1937, Codman proposed a method of subperiosteal resection with collapse of the cavity. His procedure is shown in Figure 110, which is taken from the original report (*Surg., Gynec. & Obst.* 64:485, 1937). In effect, it amounts to a complete unroofing of the cavity produced by the tumor and in other respects is similar to a complete extirpation by curettage. It has the advantage of overcoming a persistent cavity in the bone which does not always fill in with new bone even though it is packed full of bone chips. It interrupts, beyond any question, the pulsating sponge of tissue which continues to destroy bone by steady expansion.

While the author has not deliberately followed Codman's procedure, he has, in two instances of giant cell tumor seen after previous failure to cure by curettage, accomplished the same end result by unroofing the cavity,

clearing up the infection that was present, and skin-grafting the granulating surface of the cup-shaped depression in the bone. Both of these cases secured excellent results and were followed for a number of years. This

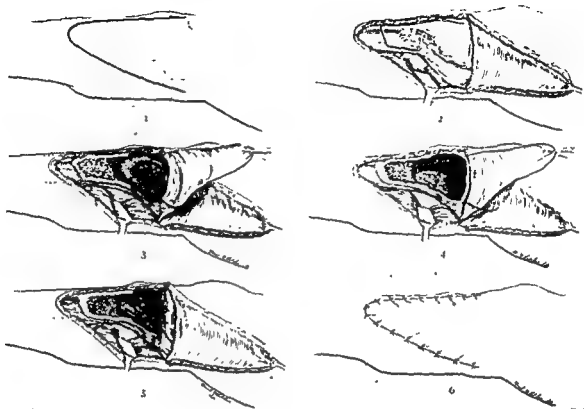


FIG. 110. Codman's operation for selected cases of giant cell tumor.

operation, particularly in cases involving the upper tibia, has merit and should receive further trial.

AMPUTATION

While in the past not a few giant cell tumors of the long bones came to amputation, this radical step was usually taken because of fungation and infection following wound-packing after curettage or following the implantation of radium in the cavity. Now that wound closure *without drainage* of any sort is the rule, only cases of benign tumors undergoing sarcomatous degeneration come to amputation. In addition, amputation has had to be employed occasionally because of the sequelae of complications incident to radiation therapy, e.g., radiation osteitis with fracture and non-union, ulceration and radiation necrosis with slough.

Amputation, as a primary method of treatment, is justified only when there is microscopic evidence of malignancy. The accompanying table will furnish some idea of the reasons for employing amputation in a group of giant cell tumors.

TABLE XVI
ANALYSIS OF TWENTY-SIX CASES OF GIANT CELL TUMOR
IN WHICH AMPUTATION WAS PERFORMED*

SECONDARY AMPUTATION (24 CASES)	TYPE OF PREVIOUS TREATMENT		
	Surgery	Radiation	Combined
For infection	2	0	2
For radiation changes	■	4	2
For malignant transformation	1	0	6
For failure to control disease	2	3	2
Total	5	7	12
Percentage of followed cases	17%	17%	37%

* Primary amputation was performed in 2 cases, secondary in 24

PROGNOSIS

The outcome in a given case of giant cell tumor is seldom predictable with certainty for it hinges upon a number of variable factors; the age of the patient, the bone (and even the portion thereof involved), the method of treatment, and most important of all, the cellularity of the stroma together with the rate and character of the growth.

It has been our experience that the older the patient is at the onset of the disease, the more uncertain is the outlook.

The sites which as a rule offer the most uncertain prognosis are the bones adjacent to the knee (these comprise about one-half of all giant cell tumors) whereas the smaller long bones or those in the upper extremity give a more favorable prognosis.

As already mentioned, the most important factor of all is the histology of the tumor. Jaffe, in his grading of these tumors, has succeeded in defining certain criteria which enable him to decide the probable clinical course of the disease (see pp. 180-181).

It should be borne in mind that some of these tumors which have not responded to treatment according to expectations or have recurred, may have undergone an alteration in their structure. This will be revealed in later microscopic sections; the outlook has, of course, changed correspondingly.

Finally it should be mentioned that where treatment by roentgen therapy has been given without microscopic examination, the diagnosis being made solely on roentgenographic appearance, the case may not respond according to expectations because the tumor is a central chondrosarcoma or osteolytic osteogenic sarcoma.

Some concept of the prognosis with different treatments may be gained from the following tabulation:

TABLE XVII
RESULTS OF TREATMENT OF 124 CASES OF GIANT CELL TUMOR

TREATMENT	CASES	RESULT EXCELLENT	RESULT GOOD	RESULT POOR	UNCLASSIFIED*
Surgery alone	35	17 (57%)	6 (20%)	7 (23%)	5
Radiation alone	53	14 (34%)	12 (30%)	15 (36%)	12
Surgery and radiation combined	34 ^b	7 (22%)	8 (25%)	17 (53%)	2
Coley's toxins alone	2	1 (50%)	1 (50%)		

* The unclassified results were deducted from the total number before the percentages were computed.

^b Of these 34 cases, 30 had postoperative radiation. In only 4 cases was preoperative radiation used. Of the latter, there was a recurrence requiring a second operation in 1; in another, malignant degeneration developed shortly after curettage, amputation was performed and death from metastases ensued.

ATYPICAL AND MALIGNANT GIANT CELL TUMOR

The typical giant cell tumor is well recognized as a lesion which, although benign, is locally invasive and may recur after treatment. Its most frequent site is the epiphyseal or metaphyseal region with extension in advanced cases into the adjacent diaphysis. Save for rare exceptions, the lesion is subcortical in origin and tends to destroy cancellous bone. As it progresses, the cortex is reduced to a thin shell or it may disappear entirely leaving the periosteum as a limiting membrane to offer resistance to encroachment upon the overlying soft parts.

Distinctly atypical cases are rarely encountered. However, the importance of recognizing them is obvious for unless their true nature is appreciated the proper treatment cannot be carried out.

Atypical giant cell tumors may be divided into two groups: (1) atypical because of clinical and pathologic criteria; and (2) atypical because of location.

The first group includes those giant cell tumors that are malignant at the time of first observation, the diagnosis being based on a study of tissue removed prior to the administration of any form of treatment, and also those tumors that are believed to have undergone malignant transformation following unsuccessful treatment by curettage, irradiation, or both.

In the second group is found that rare example of an expanding osteolytic lesion involving the shaft of a long bone rather than the epiphysis. The roentgenographic appearance does not simulate that of a malignant tumor although from its location a benign giant cell tumor is not suspected. Under conservative surgery or irradiation, this lesion responds in the manner of a giant cell tumor and sections of tissue are so diagnosed by the pathologist, although in some instances a diagnosis of "angioma of bone" may be returned. In these cases there may be reactive hyperplasia with fibrosis and giant cell areas.

As to the importance of these atypical giant cell tumors, it is obvious

that those that are malignant from the outset should be recognized and treated accordingly. This implies the use of radical surgery with or without preliminary irradiation.

In the more frequently observed examples of malignant transformation of a benign tumor, the factors that have led to such alteration of growth deserve careful consideration. It must be acknowledged that a completely satisfactory explanation of the cause or causes of this alteration has never been offered. In collaboration with Stewart and Farrow, the author reviewed the records of Memorial Hospital and the Hospital for Special Surgery and found 7 unquestionable examples of malignant transformation of a previously benign giant cell tumor.

When the tumor occupies an atypical location it is essential that its benign nature be recognized so that conservative treatment can be employed. In 1 such case personally observed, a recurrence took place after biopsy and incomplete removal; irradiation, however, yielded an excellent result. It seems not unlikely that, in the past, amputation may have been performed for such tumors under the mistaken impression that the lesion was an osteogenic sarcoma of osteolytic type.

It seems well to call attention again to the variety of tumor known as *Codman's epiphyseal chondromatous calcifying giant cell tumor*, or *benign chondroblastoma* (Jaffe) (see p. 112). Codman collected a number of examples in the upper end of the humerus. We have also observed some that were situated in the upper tibia and lower femur and no doubt they may be found in other locations as well. They often suggest chondrosarcoma, and we know of at least one instance prior to Codman's description of this lesion in which a shoulder joint disarticulation was performed in the belief that the latter diagnosis was correct. A histopathologic study of tumor tissue is the only certain means of avoiding such an error.

Other atypical cases are occasionally seen in which a bubblelike protrusion of the thinned-out cortex is present. This makes the bulk of the tumor lie outside of the normal outline of the bone, and, in our experience, the correct diagnosis in such cases is not generally made from roentgenographic examination alone (see Figs. 88, 89, and 90, pp. 72-74).

MALIGNANT GIANT CELL TUMOR—GIANT CELL SARCOMA

That there is a giant cell tumor which is clinically as well as histologically malignant at the time of first observation is no longer denied by leading pathologists.

The question of possible transformation of a benign giant cell tumor into a malignant sarcoma has been discussed for more than a century and has aroused the interest of practically every worker in this field. It is now conceded that some giant cell tumors may at first exhibit all the characteristics of a benign lesion, but later become increasingly aggressive and

TABLE XVII

RESULTS OF TREATMENT OF 124 CASES OF GIANT CELL TUMOR

TREATMENT	CASES	RESULT EXCELLENT	RESULT GOOD	RESULT POOR	UNCLASSIFIED ^a
Surgery alone	35	17 (57%)	6 (20%)	7 (23%)	5
Radiation alone	53	14 (34%)	12 (30%)	15 (36%)	12
Surgery and radiation combined	34 ^b	7 (22%)	8 (25%)	17 (53%)	2
Coley's toxins alone	2	1 (50%)	1 (50%)		

^a The unclassified results were deducted from the total number before the percentages were computed.

^b Of these 34 cases, 30 had postoperative radiation. In only 4 cases was preoperative radiation used. Of the latter, there was a recurrence requiring a second operation in 1; in another, malignant degeneration developed shortly after curettage, amputation was performed and death from metastases ensued.

ATYPICAL AND MALIGNANT GIANT CELL TUMOR

The typical giant cell tumor is well recognized as a lesion which, although benign, is locally invasive and may recur after treatment. Its most frequent site is the epiphyseal or metaphyseal region with extension in advanced cases into the adjacent diaphysis. Save for rare exceptions, the lesion is subcortical in origin and tends to destroy cancellous bone. As it progresses, the cortex is reduced to a thin shell or it may disappear entirely leaving the periosteum as a limiting membrane to offer resistance to encroachment upon the overlying soft parts.

Distinctly atypical cases are rarely encountered. However, the importance of recognizing them is obvious for unless their true nature is appreciated the proper treatment cannot be carried out.

Atypical giant cell tumors may be divided into two groups: (1) atypical because of clinical and pathologic criteria; and (2) atypical because of location.

The first group includes those giant cell tumors that are malignant at the time of first observation, the diagnosis being based on a study of tissue removed prior to the administration of any form of treatment, and also those tumors that are believed to have undergone malignant transformation following unsuccessful treatment by curettage, irradiation, or both.

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finally reveal roentgenographic and microscopic features of malignancy with pulmonary metastasis and fatal termination. An unsatisfactory response on the part of a benign giant cell tumor to the accepted methods



FIG. 111. Malignant degeneration of a giant cell tumor which was benign on microscopic examination at the first operation—curettage. The final procedure was a hip disarticulation. (Army & Navy General Hospital.)

of treatment skillfully carried out should at once warn the clinician of the possibility of such an alteration.

In attempting to ascertain the cause of such malignant transformation, we note from a study of our personal series that most of the cases had been treated by a combination of surgical and radiation methods, or by curettage without primary wound closure. In a series of 7 cases of malignant giant cell tumors, 4 were treated with both curettage and radiation therapy and 3 by curettage alone, 1 of the latter cases and 1 of those treated by X-ray and curettage had packing with gauze in place of primary closure. This is a method which is deplorable and inexcusable. These 7 cases had a total of seventeen curettages. One patient had no less than six, interspersed with four courses of roentgen therapy.

When a case is curetted and the first tissue report is benign giant cell

tumor and a recurrence takes place, another curettage is justified if the lesion is not situated where a resection is feasible. If the material obtained from the second curettage shows an aggressive or borderline tumor the patient must be kept under rigid observation, and amputation must promptly follow a second recurrence should the report indicate further transition toward a frankly malignant tumor. In the effort to avoid an amputation, one must not defer it too long (see Fig. 111).

We are of the impression that an apparently well-controlled lesion may, as a result of later injury, develop recurrence and even undergo malignant transformation. It is well, therefore, to caution a patient that has recovered from a giant cell tumor that injury to the affected area may have serious consequences.

The whole question of the transformation of benign giant cell tumor into sarcoma has received extensive discussion from the time of Astley Cooper, Paget, and Nelaton all the way down to Bloodgood, William B. Coley, Ewing, and Stewart. It seems that until more is known of the nature of the circumstances, physical and biochemical, that have initiated the tumor and of the extrinsic factors that affect its normal development, any explanation of the malignant evolution of a giant cell tumor is largely conjectural. /

Diagnosis

The diagnosis must rest upon the opinion of a well-trained pathologist who has had an opportunity to examine sections obtained from an open biopsy. It requires unusual experience and skill to make a distinction between a benign, a borderline, and a malignant giant cell tumor on the basis of a smear from an aspiration biopsy.

While roentgenographic examination is usually suggestive of an aggressive or a possibly malignant giant cell tumor, seldom is a correct diagnosis made from films alone.

In a patient with a microscopically confirmed giant cell tumor treated with surgery or radiation, alone or in combination, the return of symptoms after a free interval of months to several years is strongly suggestive of malignant degeneration. This is especially true if there has been an injury which could have caused reactivation.

Treatment

Malignant giant cell tumor calls for treatment as a malignant rather than a benign lesion. Except in those localities where a wide local removal is possible (upper fibula or patella) an amputation is required. Whether or not the operation is preceded by irradiation is a matter of opinion; however, these tumors have not been found to be radiosensitive and hence an immediate amputation is preferred.

Prognosis

The prognosis of malignant giant cell tumor is that of a true sarcoma and not of giant cell tumor in general. Too few cases have been seen and few clinicians have had a sufficiently wide experience upon which to base statistical estimates of five-year survivals. It is our impression that only 10 to 15 per cent survive for a period of five years after the tumor has been recognized as malignant.

So far as we are aware no case of malignant giant cell tumor treated by irradiation alone has survived five years.

CASE REPORTS

Case 1

J.K.McC., female, age 18 years, was admitted to Memorial Hospital on July 25, 1929, with a history of pain in the left shoulder of seven months' duration. The pain was constant and grew progressively worse; it was made more acute by activity. The left shoulder was held in a protective attitude.

Examination showed the left shoulder to be the site of a symmetrical swelling which made it appear much larger than the right shoulder. There was moderate tenderness to pressure but no muscle spasm, the movements being limited by pain. The surface temperature was recorded as being increased in this shoulder.

As a result of the history and physical findings a provisional diagnosis of osteogenic sarcoma was made.

Roentgenograms made on July 25, 1929, were reported by Dr. Ralph E. Herendeen as follows: "No evidence of metastases seen in the film of the lungs. Stereo views of the left shoulder reveal evidence of a destructive process involving the upper end of the humerus. It appears to be medullary in origin, but the growth has been so rapid that very little dilatation of the medullary portion has taken place, without any evidence of an attempt at limitation through the callous production. The medullary portion of the shaft below this area is altered in density and it appears that this portion is involved also, although some of the loss of bone density may be due to atrophy of disuse. X-ray diagnosis: Malignant primary medullary bone tumor."

Without waiting for histologic confirmation a disarticulation through the left shoulder-joint was carried out. The wound healed by primary union. The report of the pathologist was that of benign giant cell tumor. Following the operation the patient returned to her home in the South. Three years later it was learned that a recurrence had taken place in the left scapula. The scapula was then removed by Dr. M. O. Ewing of Amory, Mississippi, in May, 1932. Tissue forwarded to Memorial Hospital was examined by Dr. Fred Stewart who rendered the following report: "The bulk of this shows giant cell tumor; however, portions are laying down bone, other parts have lost giant cells and the tumor is malignant."

Dr. Stewart further commented in a report to Dr. Ewing, as follows: "In the first specimen the process resembles in every way a giant cell tumor histologically. It is of the telangiectatic type—the so-called benign bone aneurysm type. The

only unusual feature consisted in the prolongation of the tumor into the shaft in the gross specimen. This should arouse suspicion at once. Now in the second specimen much of the tissue is still benign giant cell tumor. Part of it represents the stage which we have repeatedly seen in giant cell tumors which show progressive malignant change in each recurrence and eventually metastasize. I think the second lesion was an 'implant' by way of the veins. This patient may remain well but is not yet out of the woods."

Fortunately the subsequent history of the patient shows that her health has remained excellent; she is at present (1948) teaching in a college in Missouri. She reported to the Follow-up Clinic at Memorial Hospital on July 24, 1946, and examination revealed no evidence of disease.

Comment: This case presents the following features which deserve consideration: (1) It illustrates the danger of relying solely upon clinical and roentgenographic evidence for a diagnosis of malignant tumor of bone without having recourse to histologic confirmation. (2) It represents one of the cases in which a giant cell tumor spreads to another bone (probably by way of the veins as suggested by Dr. Stewart), and this, in our opinion, is an exceedingly rare complication. The tumor in the scapula had already undergone malignant alteration and one can reasonably assume that had the primary tumor been treated by curettage it would have recurred and a malignant transformation would have taken place. Where such transformation has been observed the majority of the patients have eventually succumbed to metastases, usually, however, after more than one attempt at conservative surgery has been carried out. One is entitled to speculate that in this case the amputation and later scapulectomy resulted in a survival of more than seventeen years.

The following case emphasizes the harmful effects of excessive doses of radiation therapy in giant cell tumor:

Case 2

G.N., male, age 40, was admitted to Memorial Hospital on Sept. 16, 1931, with the diagnosis of giant cell tumor, lower end of left radius (see Fig. 112A).

Treatment: Roentgen Therapy:

1. At another institution from Mar. 19 to Apr. 17, 1931: 2850 r to each of 2 portals.
2. At Memorial Hospital from Sept. 16 to 18, 1931: 600 r to each of 2 portals.
3. At Memorial Hospital from Oct. 26 to 29, 1931: 600 r to each of 2 portals.
4. At Memorial Hospital from Feb. 25 to 27, 1932: 600 r to each of 2 portals.

We have estimated that the center of the tumor received a total dose from these treatments of nearly 7000 r.

Effects of Treatment: The tumor decreased in size and appeared to be controlled but the bone did not regenerate (see Fig. 112B). Deformity developed consisting of radial deviation of hand and prominence of ulnar styloid. Four years after the first treatment a spontaneous fracture through the irradiated portion of the ulna resulted in a correction of this deformity. During the next twelve

years, the patient was able to use the wrist fairly well but telangiectasia and sclerosis of soft tissue in the irradiated area became marked (see Fig. 112C and D).

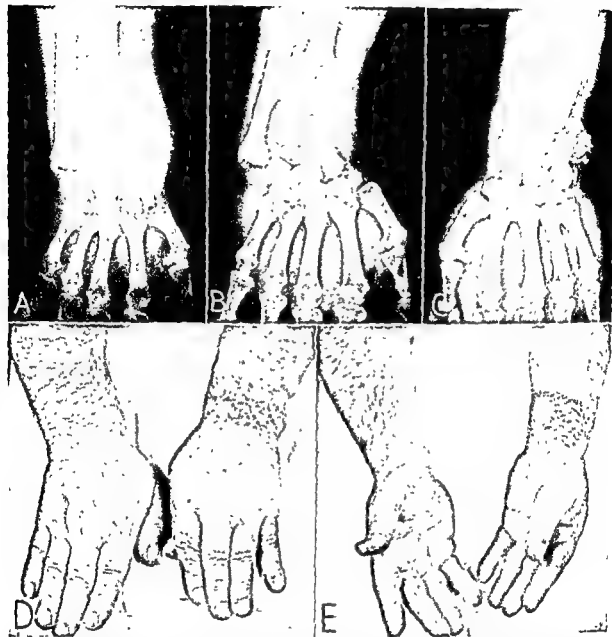


FIG. 112 A, Roentgenogram of extensive giant cell tumor of radius prior to treatment. B, Same case one year after roentgen therapy. Although the tumor is smaller, there has been no bone regeneration. C, Same case sixteen years later. Note the pathologic fracture of lower end of ulna brought about by damage to bone as a result of roentgen therapy. A pseudarthrosis has replaced the normal wrist bone. D and E, Changes in skin of wrist as a result of repeated and prolonged heavy roentgen therapy.

By January, 1947 it was apparent that an excision of the damaged skin would be required. He was, therefore, admitted to the Hospital for Special Surgery on Feb. 2, 1947. The left wrist showed shortening, deformity, limited motion, and marked loss of power. The hand and fingers were quite edematous. A band of dense scar tissue encircled the wrist like a bracelet and was firmly attached to

the underlying extensor tendons. Telangiectasia, scarring, crusting, and beginning ulceration were additional features.

Plastic operations were used to cover the area following complete excision of the circular band of devitalized skin. The abdomen was the site of the bipedicle flap used to cover the dorsum, while to the volar aspect of the wrist a split-thickness graft was applied.

The accompanying photographs give a better conception of the sequence of events in this case than can be gained from a written description.

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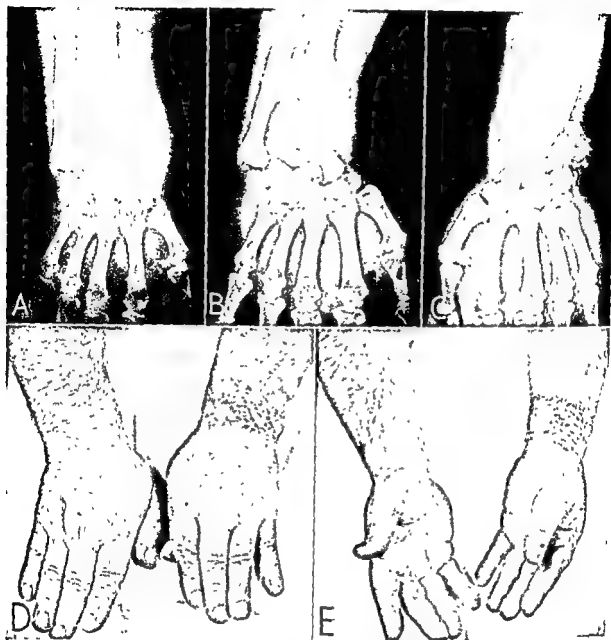


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18. ADAMANTINOMA

PRIMARY ADAMANTINOMA OF LONG BONES

THE FACT THAT ADAMANTINOMA OF THE LONG BONES HAS BEEN RECORDED in only 18 instances places it as one of the rarest of primary bone neoplasms; the tibia was the affected bone in 17 cases and the ulna in 1 (see Fig. 113). When this tumor affects the jaws, it arises from the basal cells of primitive tooth buds (ameloblasts). Theories of its origin in such remote locations as the long bones are not wholly satisfying. Fischer explained these cases on the basis of origin from cell rests implanted early in fetal life; he believed that if the cells were implanted later they would not possess the power of differentiating into toothlike tissues and squamous epithelium would result.

Ryrie, on the contrary, considered that these tumors originated from basal cells of the skin which, as a result of trauma, had become implanted in bone. Some support is afforded Ryrie's theory by the high incidence of a definite history of severe injury at the site of the ultimate development of the tumor. It is difficult to conceive of the type of trauma which could deposit cells of dermal origin beneath the periosteum and in the cortex without leaving some roentgenographic evidence of bone damage or periosteal proliferation such as is seen in cases of subperiosteal or parosteal ossifying hematoma (myositis ossificans) or the cortical thickening seen in incomplete fractures. Without a break in the periosteum or cortex, both, it is not easy to visualize the implantation of epithelial elements from the skin appendages (sweat glands, hair follicles, or sebaceous glands).

Anderson and Saunders offer an attractive theory that the "environment," i.e., bone, in which the basal cells are implanted, is the determining factor in their differentiation into ameloblasts to form an adamantinoma tumor and suggest that experimental work in the field of animal research and tissue culture might yield some enlightenment.

CLINICAL FEATURES

Adamantinoma of long bones, like that of the jaws, arises in the mandible, is a tumor of locally invasive properties but lacks the power to produce

distant metastases; thus it is cured by complete removal of the tumor-bearing area. Its growth is essentially slow although recurrences after operation sometimes exhibit increased growth rapidity. As might be anticipated.



FIG. 113. - Primary adamantinoma of tibia.

the symptoms are not severe and may be insignificant until the growth reaches considerable size. Pain is transitory and may not be associated with swelling, tenderness, or dysfunction; later it becomes aching in character, but there may be intervals with complete freedom from symptoms.

When the swelling becomes pronounced enough to attract the patient's attention, a physician is consulted, roentgenographs are taken, and the presence of a bone lesion confirmed. As in jaw cases, adamantinoma of the



FIG. 114. Adamantinoma of ulna. (Courtesy of Anderson, C E., and Saunders, J. B.; see Bibliography.)

long bones is a disease of long duration, even as long as twenty years. The superficial location of the tibia favors trauma as the exciting cause. We know of no other bone neoplasm which occurs almost exclusively in one particular bone. Some anatomic reason for this selectivity is certainly suggested.

TREATMENT

The early case, in which complete extirpation of the tumor-bearing area is possible, should have adequate block resection or segmental resection

and bone graft. Complete excision at the initial operation is essential for, if recurrence takes place, subsequent conservative measures are very likely to fail and amputation will be required. Of the 18 collected cases, ampu-

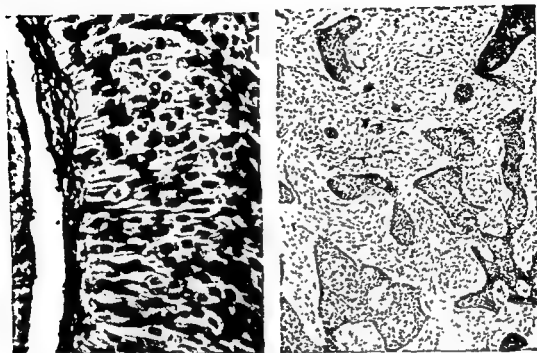


FIG. 115. Microphotographs of adamantinoma of ulna: *left*, high power; *right*, low power.

tation was required in 6 and seems to have been indicated in at least 3 others. Curettage initially was done in 6 cases, with recurrence in all; it has no place in the treatment of this disease. On the other hand, in the 3 tibia cases where resection and bone graft was done, none recurred; however, 1 case in the ulna did recur (see Figs. 114 and 115).

Following an apparently successful operative removal the patient should be cautioned that regular follow-up roentgenographic examination at six-month intervals is essential. Because of the silent and symptomless manner in which this tumor can extend, recurrence can occur and progress insidiously beyond the scope of conservative surgery unless detected by study of serial roentgenograms.

Table XVIII lists the cases of adamantinoma of long bones published up to January, 1946, as compiled by Hebbel (1940), Dockerty and Meyerding (1942), and Anderson and Saunders (1942). It will be noted that in Cases Nos. 1 to 17 inclusive the disease occurred in the tibia while in Case No. 18 the ulna was involved. The author is indebted to Anderson and Saunders for the privilege of reproducing their illustrations of the only known case of adamantinoma occurring in a long bone other than the tibia.

For a discussion of adamantinoma of the jaws, see the Chapter in Section Four, "Tumors of Bone in Special Localities," page 429.

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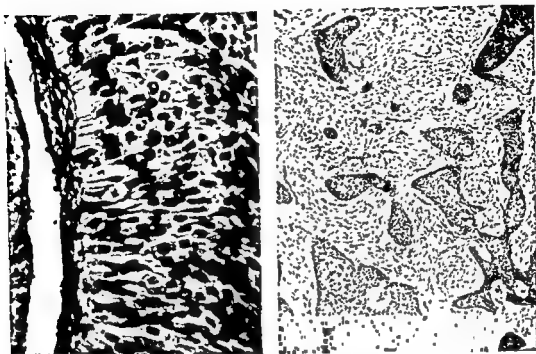


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TABLE XVIII
SUMMARY OF CASES OF ADAMANTINOMA OF LONG BONES

CASE	YEAR	AUTHOR	AGE, YRS	SEX	SITE	ANTECEDENT TRAUMA	LATENT PERIOD	CHARACTER & DURATION OF SYMPTOMS	INITIAL THERAPY	SUBSEQUENT COURSE
1*	1913	Fischer	37	M	Junction lower and middle 3ds, left	Contusion	5 mo.	Pain, swelling, 5 mo.	Resection; bone graft	No recurrence 8 mo. later
2	1930	Richter	12	M	Middle 3d, left	Fall	?	Swelling, 8 mo.	Amputation	Uneventful
3	1931	Baker & Hawksley	46	M	Lower 3d, left	Contusion	8½ mo.	Pain, swelling, 6 wk.	Resection; bone graft	No recurrence 2 mo. later
4	1932	Ryrie	52	M	Middle 3d.	Contusion	8 yr.	Swelling, 8 yr.	Curettage	Recurrence; amputation 6 mo. later
5	1933	Petrov & Glasunow	22	M	Middle 3d., left	None	None	Swelling, 3 yr.	Resection; bone graft	No recurrence 1 yr. later
6	1934	Holden & Gray	36	F	Lower 3d, left	Abrasion, contusion of ankle	None	Pain, 2 yr	Excision	Recurrence after 2 yr.; reexcision; roentgen therapy of high voltage
7	1937	Bishop	22	M	Upper 3d, right	Fracture	8 wk.	Swelling, 3 yr.	Curettage, chips, graft	Recurrence; amputation after 14 mo.; 4 yr. after fracture
8	1938	Rehbock & Barber	24	F	Lower 3d, left	Sprain of ankle	None	Pain, swelling, 18 mo.	Wide excision	No recurrence 8 mo. later
9	1938	Oberling, Vermees, & Chevreau	51	M	Middle 3d.	?	?	?	Excision	Recurrence, amputation 7 mo. later
10	1938	Dunne	32	M	Junction upper and middle 3ds, left	Contusion, abrasion	9 mo.	Swelling, 4 yr.; pain later months	Roentgen therapy of high voltage	Progression; amputation 9 mo. later

11	1938	Wolfert & Sloane	57	F	Junction middle and lower 3ds, left	Contusion	None	Swelling, 19 mo; pain 4 mo.	Excision	Recurrence in 16 mo.; resection; no further recurrence 47 mo. after first operation
12	1938	Wolfert & Sloane	18	F	Lower half, right	Abrasion	3½ yr	Pain, 4 mo.	Curettage, radium	Recurrence; resection 13 mo. later; recurrence; amputation after 12 mo.
13	1939	Thomas	19	F	Upper right	None	None	Swelling, 7 yr.; pathologic fract.	Curettage, graft	Recurrence; amputation 8 mo. later
14	1939	Rankin	25	M	Lower left	Puncture wound	1 yr.	Pain, swelling, 1½ yr.	Curettage	Recurrence; excision 15 mo. later; no recurrence 2 yr after first operation
15	1939	Hebbel	14	F	Lower right	None	None	Pain, swelling, 4 mo.	Curettage	Recurrence; curettage 15 mo. later; recurrence, amputation 2½ yr. after onset
16	1941	Dockerty & Meyerding	24	F	Left middle	?	None	Recurrent pain, 8 yr.; swelling, 4 yr.	Excision	Recurrence; amputation 15 mo. later
17	1941	Dockerty & Meyerding	27	M	Left middle	Abrasion	6 yr.	Recurrent fractures; pain; tumor	Repeated excision; roentgen therapy	Arrested (?) 16 mo.
18	1942	Anderson & Saunders	45	M	Ulna, entire shaft	Series of injuries	17 yr.	Recurrent fractures, pain, swelling	Resection; bone graft	5 yr. later another resection incomplete

*Cases 1 through 15 from HIZBET, R. Adamantinoma of the tibia. *Surgery* 7:860, 1940

†Cases 16 and 17 from DOCKERTY, M. B. and MEYERDING, H. W. Adamantinoma of the tibia, report of two new cases. *J. A. M. A.* 119:912, 1942

19. CHORDO

WHILE IT IS RECOGNIZED THAT THESE TUMORS OCCUR IN OTHER LOCATIONS than the sacrococcygeal area it was considered advisable to place the pages dealing with them in the Chapter devoted to "Tumors of the Pelvic Bones" (see p. 448).

20. SARCOMA AS LATE DEVELOPMENT IN BENIGN LESIONS OF BONE

SARCOMA ARISING ON THE BASIS OF BENIGN TUMORS AND ALLIED LESIONS OF bone is referred to in the chapters dealing with the particular conditions. The fact that this serious late complication does arise in a variety of bone conditions is probably not widely recognized and it is of great importance that clinicians dealing with them should appreciate this possibility and be able to recognize it promptly.

Some bone lesions are fairly common sites of this sarcomatous degeneration, e.g., chondroma, Paget's disease, and giant cell tumor. Others are rare, e.g., bone cyst and fibrous dysplasia; still others are of extreme rarity, e.g., myositis ossificans (ossifying hematoma), osteopetrosis, osteoid osteoma, and Gaucher's disease involving bone.

The cause of this malignant change is a matter of conjecture. However, we have been much impressed with the fact that preceding this change the area of sarcomatous development had been subjected to rather heavy roentgen therapy in a number of instances including all 3 of the bone cysts, 2 of the fibrous dysplasias, the osteoid osteoma, and a number of the giant cell tumors. That a time interval of from four to fifteen years is likely to occur is evident from a study of the clinical records of these cases. Moreover, in the case of the chondromas we have observed that the malignant change seldom occurred before middle or later adult life even though the chondroma's presence had been noted for many years and in all probability had existed from birth.

Our experience with this form of secondary sarcoma leads us to conclude that: (1) Roentgen therapy is not advisable for accessible giant cell tumor or for unicameral bone cyst. (2) Benign cartilage tumors constitute a future hazard and their removal is sound preventive treatment. (3) Patients with Paget's disease and fibrous dysplasia must be kept under close

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WHILE IT IS RECOGNIZED THAT THESE TUMORS OCCUR IN OTHER LOCATIONS than the sacrococcygeal area it was considered advisable to place the pages dealing with them in the Chapter devoted to "Tumors of the Pelvic Bones" (see p. 448).

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Our experience with this form of secondary sarcoma leads us to conclude that: (1) Roentgen therapy is not advisable for accessible giant cell tumor or for unicameral bone cyst. (2) Benign cartilage tumors constitute a future hazard and their removal is sound preventive treatment. (3) Patients with Paget's disease and fibrous dysplasia must be kept under close observation for possible sarcomatous change. (4) Certain other bone abnormalities may at times provide the site for such a change.

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SECTION THREE

Primary Malignant Tumors of Bone

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INTRODUCTION TO SECTION THREE

AS IS IMPLIED BY THE TERM MALIGNANT, ALL TUMORS DISCUSSED IN THIS section have in common the following characteristics: (1) Absence of capsular definition, (2) progressive growth, (3) ability to extend locally by infiltration of surrounding tissues, (4) tendency to bleed, fungate, or recur after incomplete operative interference, and (5) power to disseminate to distant parts by metastasis and to cause the death of the patient. The rate of growth and the tendency to recur and to spread to other organs vary considerably according to the type of tumor present, and also differ in individual tumors of the same type. For example, Ewing's sarcoma rarely fails to cause death from metastasis regardless of how the primary growth is treated, while fibrosarcoma and certain chondromyxosarcomas remain localized for long periods and may be cured if removed completely during this latent phase. Myeloma occurs in multiple foci which constitute multicentric origins of the disease.

RELATIVE FREQUENCY

The most frequently encountered lesion is osteogenic sarcoma (66 per cent), with Ewing's sarcoma next (22 per cent), and myeloma third (9 per cent). Reticulum cell sarcoma of bone furnishes only 3 per cent.

CLINICAL FEATURES

These neoplasms as a group tend to cause *pain* early in their course; the pain is persistent and increases steadily in severity. *Tumefaction* is an early symptom; the swelling progresses steadily and often rapidly. *Disability* is a constant finding although early in the disease this feature may not be prominent.

ROENTGENOGRAPHIC FEATURES

The difficulties encountered in the interpretation of roentgenograms and the possibility of errors have been discussed in an early chapter. Certain features common to most malignant tumors of bone are strongly indicative of their nature. For example, irregular bone destruction of the cortex and spongiosa (see Fig. 116), lack of sharp outline in the affected area, tend-

ency to destroy without much expansion of the bone (see Fig. 117), formation of osteoid or calcified tumor tissue beyond the normal confines of the bone (see Fig. 118), the reactive bone at the margin of the advancing



FIG. 116. Medullary fibromyxosarcoma of upper femur, amputation and microscopic confirmation. Patient was an elderly male.

tumor (Codman's triangle) (see Fig. 119), splitting or lamellation of the cortical bone (onion-skin appearance), and laying down of spicules of new bone at right angles to the shaft (sun-ray appearance) (see Fig. 120) are all criteria strongly suggestive of malignancy.



FIG. 117. Osteogenic sarcoma. The entire thickness of the femur is involved with the extension beyond mid-shaft.

PATHOLOGIC FEATURES

There is a considerable variation in the gross and microscopic features of some of the malignant bone tumors, notably osteogenic sarcoma, chondrosarcoma, and malignant giant cell tumor. Ewing's sarcoma, reticulum cell sarcoma, and multiple myeloma are much more uniform in their microscopic appearance and do not lend themselves to an histologic grading. Attempts have been made to grade osteogenic and chondrosarcoma according to their degree of malignancy and solely on their histologic features. We are not con-

vinced that a gradation which is carried to the extent of subdividing these

tumors into as many as four groups serves any useful purpose. It is distinctly worthwhile, however, to recognize those tumors that are histologically of low-grade malignancy. We prefer to place all others in a single group that



FIG. 118

FIG. 118. Osteogenic sarcoma. Biopsied as a bone infection but proximal to involved area. Transferred to a general hospital as case of osteomyelitis. Patient a 20-year-old male. Finally amputated at McCloskey General Hospital.



FIG. 119

FIG. 119. Osteogenic sarcoma, osteolytic form, with high degree of malignancy in a girl of 5. Radiation caused marked regression but failed to control the growth and amputation was performed. The survival for thirteen years makes this a unique case in view of the patient's age and the histologic character of the tumor.

may be termed *sarcomas of average malignancy*. Stewart attempted to separate the series reported by Pool and the author into the following: *low-grade*, *average*, and *high-grade* malignancy, but we found that while the prognosis for the *low-grade* tumors was much more favorable, that for the *average* and *high-grade* was virtually identical. It should be pointed out that occasionally tumors which appear to be of extremely low-grade malignancy

nancy at the time of the first biopsy may, after repeated, unsuccessful attempts to eradicate them, assume increasingly more atypical cellular features necessitating a change of grading. Frequently our pathologists have



FIG. 120. Osteogenic sarcoma. Note the irregular destruction and also the increased density; and the "sun-ray" appearance which is best seen in the anteroposterior view. (Borden General Hospital.)

reported that a given tumor while maintaining its present histologic features would not be expected to metastasize, and we have been repeatedly impressed with the accuracy of these prognostications. In our experience it is a rare occurrence to encounter metastasis in a case in which the pathologist

2I. OSTEOGENIC SARCOMA

THE DESIGNATION OSTEOGENIC SARCOMA IS NOW WIDELY RECOGNIZED AS A generic term for the most common of the primary malignant neoplasms derived from bone. It includes a number of tumors which differ in their site of origin, gross morphology, rate of growth, roentgenographic appearance, and even in their response to treatment and ultimate prognosis. Some have questioned the validity of the term used in this sense, claiming that it may signify sarcoma *producing* bone, yet its use by the Committee of the Bone Sarcoma Registry of the American College of Surgeons (following Webster's dictionary) has been generally accepted to signify tumors originating in bone.

This group includes varieties which in the older nomenclature were termed *periosteal sarcoma*, *osteosarcoma*, *central* or *medullary sarcoma*, or *polyhedral cell sarcoma*.

CLASSIFICATION

The revised classification of the Bone Sarcoma Registry Committee of the American College of Surgeons lists the subdivisions of osteogenic sarcoma as follows:

1. Medullary and subperiosteal
2. Telangiectatic
3. Sclerosing
4. Periosteal
5. Fibrosarcoma
 - a. Medullary
 - b. Periosteal
6. Capsular and parosteal

The separation of sarcoma of cartilaginous origin is an important feature of this revised classification; previously, chondrosarcoma was included with the osteogenic group. Phemister, in 1930, was one of the first to emphasize the need for this distinction. It now seems that this separation of chondrosarcoma is on an anatomic and clinical basis beyond dispute. Certainly this is true of the so-called secondary chondrosarcoma. These cartilage-derived sarcomas will be discussed later.

It would seem to us equally important to remove from the osteogenic group the fibrosarcomas, both medullary and periosteal as well as the parosteal and capsular forms, for there is nothing to indicate that these tumors arise from cells that are of the bone-forming series, and it is justifiable to ascribe them to cells destined to form connective or supporting tissue. It is commonly known that these fibrosarcomas have a distinctly different clinical course and that the prognosis is measurably better than in other types of osteogenic sarcoma. Therefore we feel that they should not be classified as a subgroup of osteogenic sarcoma but should be placed in a separate group. This is in keeping with the views of other authorities and with the earlier classification of the Bone Sarcoma Registry.

Ewing was instrumental in the further separation of osteogenic sarcoma into periosteal, medullary and subperiosteal, telangiectatic, and sclerosing types. This seems to us of doubtful value and of somewhat uncertain justification. These terms are largely based upon gross pathology and are not clearly defined. While the individual tumor may present features that would justify its inclusion in several of these sub-groups, histologic features are not capable of separation into these same sub-groups. In short, the value of this separation, from a prognostic or therapeutic standpoint, is highly questionable. To use the terms osteogenic sarcoma, chondrosarcoma, fibrosarcoma, without further subdivision seems more logical, less confusing, and therefore more desirable.

Non-bone-forming tumors that are parosteal or capsular should probably be regarded as *fibrosarcoma* (see Fig. 121). This is not an attempt to include those primary malignant tumors of joint, bursal, or tendon sheath origin, which are obviously of synovial nature—true malignant synoviomas—nor those spindle cell neurogenic or myogenic sarcomas which may occasionally encroach upon bone by direct extension from without.



vival. This is one of the relatively favorable types, affording a rather large proportion of five-year survivals.

TYPE

Medullary and subperiosteal osteogenic sarcoma is the term applied to that common form which, arising in the shaft, extends both beneath the



FIG. 122. Osteogenic sarcoma in an adolescent. Note particularly the well developed "Codman's triangle" of reactive bone at the upper margin of the tumor.



FIG. 123. Osteogenic sarcoma in a child of seven years. Note the area of increased density surrounded by a more radiolucent area of irregular bone destruction.

periosteum and into the medullary cavity (see Figs. 122, 123). It commonly forms, beneath the uplifted periosteum, that characteristic area of reactive bone formation described by Codman and often referred to as *Codman's triangle*.

Telangiectatic sarcoma of bone (sometimes referred to as *malignant bone aneurysm*), is a well defined, highly vascular tumor. Its exact relationship to certain aneurysmal giant cell tumors on the one hand and to the other tumors of the osteogenic sarcoma group is not clear. It may well belong to the angioma series and ultimately be classed as *angiosarcoma*. Further studies of this tumor may result in its removal from the present place it occupies in the classification. It is one of the less common forms. It has exceedingly malignant features with a correspondingly unfavorable prognosis.

Sclerosing osteogenic sarcoma is a clearly defined tumor with definite roentgenographic appearance. In the roentgenograms dense new bone formation is seen in the medullary cavity, the cortex, and the extra-cortical portion

of the tumor which extends into the soft parts (see Figs. 124, 125). The characteristic "sun-ray" appearance may be seen here. In some instances, growth of the tumor is more gradual and the interval elapsing between



FIG. 124. Sclerosing osteogenic sarcoma of femur. This patient developed a second primary in the humerus after the original tumor in the femur had been subjected to amputation. A third primary involved the tibia.

first symptoms and amputation is usually longer than is the case in some of the other varieties of osteogenic sarcoma. It is a radioresistant tumor. It consists of osteoid tissue heavily calcified in places with spicules of bone predominating. It offers a better prognosis than does the telangiectatic or chondroblastic sarcoma. The outlook, however, is on the whole unfavorable and metastases generally occur before surgical removal has been accomplished.

Periosteal sarcoma of bone—before the morphologic and histopathologic studies of bone sarcoma had reached the stage when a classification by the Registry was possible, the term *periosteal sarcoma* was used by clinicians and pathologists and even by the early radiologists to signify any primary malignant tumor that was not obviously of central or medullary origin. Today this term has been restricted to include only those spindle cell, non-bone-forming growths that, arising from the outer layers of the periosteum, do not destroy or produce bone and which alter the adjacent bone only by pressure from without (see Figs. 126, 127, and 128).

Periosteal sarcoma shows a marked variation in histology. Some of these

tumors are composed of cells that resemble a fibroma in their uniformity. Others have cells that exhibit all the anaplastic criteria of malignancy. Thus the capacity of this tumor to metastasize varies greatly. Many of the



FIG. 125. Sclerosing osteogenic sarcoma with considerable extension about the shaft. Note density of tumor bone, radial striations, and site of origin in metaphyseal area.

five-year survivals of osteogenic sarcoma belong in this group and a study of their microscopic sections reveals a low-grade malignancy. For this group as a whole the outlook is not favorable; metastases generally have developed before surgical removal is accomplished. Several cases have yielded favorable results from combined external and interstitial irradiation but to be adaptable to this form of treatment the tumor must be distinctly limited in its extent.

Medullary fibrosarcoma is a central tumor of relative rarity which occurs ally in the shaft of the long bones near the epiphyseal line. The roentgenographic appearance is inconsistent. In some there is irregular expan-



FIG. 126 . Osteogenic sarcoma of humerus, periosteal form. There is minimal involvement of the humeral shaft.

on of the bone resembling that seen in a central chondroma or a giant cell tumor yet the destruction of portions of the cortex is irregular. It presents some of the criteria of a slowly growing process. As a rule the symptoms are correspondingly milder and have existed for a longer period than usual in the more malignant forms. Other films resemble the osteolytic medullary sarcoma of highly malignant character (see Fig. 129). It is not possible to predict the nature of this tumor by roentgenographic examination alone.

Its relation to Paget's disease or Recklinghausen's neurofibromatosis was suggested by Ewing. It is probable that some cases which in the past have been classified as low-grade medullary fibrosarcoma actually represent either fibrous dysplasia, a healed phase of an attenuated bone infection, or an area of osteolysis from some metabolic disorder which has failed to respond by regeneration of bone.

Whatever their theoretical relation to other bone disorders may medullary fibrosarcomas are of low-grade malignancy and many are ceptible of cure by radical surgery. Any large collection of five-year vivals of osteogenic sarcoma is certain to include some cases of this t



FIG. 127. Osteogenic sarcoma, periosteal type, in an unusual location. The patient, a young girl, developed two other tumors in the bones of the opposite lower extremity. These were thought to be examples of multiple primary sarcomas rather than metastases.

Capsular and parosteal sarcomas have been included among osteogenic sarcoma with some question as to the propriety of such decision. They are encountered rarely. They occur in connection with the joint capsule or the deep fascial attachments to bone and themselves produce a bony or osteoid tissue. However intimate their relationship to bone, they do not actually arise from it. It may be exceedingly difficult to distinguish these tumors

clinically from chondroma. They must not be confused with deeply situated fascial myxosarcomas and neurogenic sarcomas arising from nerve trunks, coursing deep and in close proximity to bone. Sometimes this is a

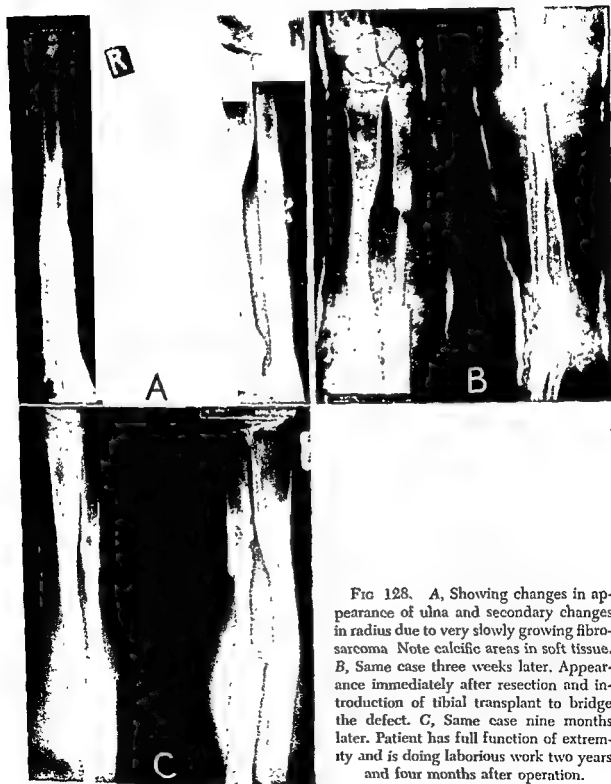


FIG 128. A, Showing changes in appearance of ulna and secondary changes in radius due to very slowly growing fibrosarcoma. Note calcific areas in soft tissue. B, Same case three weeks later. Appearance immediately after resection and introduction of tibial transplant to bridge the defect. C, Same case nine months later. Patient has full function of extremity and is doing laborious work two years and four months after operation.

delicate task even after amputation has afforded the fullest opportunity for a study of the gross as well as the microscopic features and of the relation

of the tumor to the adjacent bone or joint. Capsular tumors, although less frequently observed, may closely resemble synovioma; even with the aid of the microscope the distinction may be exceedingly difficult.

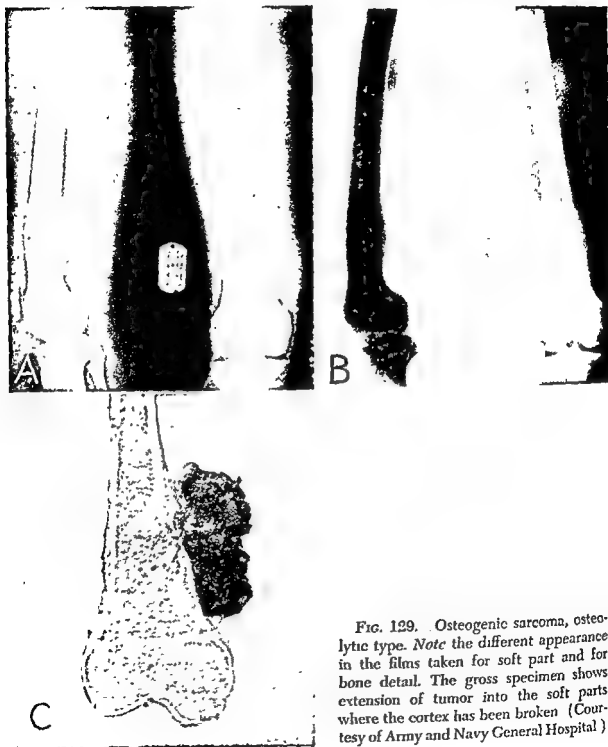


FIG. 129. Osteogenic sarcoma, osteolytic type. *Note* the different appearance in the films taken for soft part and for bone detail. The gross specimen shows extension of tumor into the soft parts where the cortex has been broken (Courtesy of Army and Navy General Hospital)

LOCATION

The majority of these tumors originate in the metaphyseal region at the ends of major long bones. In nearly two-thirds of the cases the lower extremity is involved; approximately one-third occur in the lower femur. The

upper humerus and upper tibia are the next most frequent sites. Figure 180 shows the location of 312 cases from the Memorial Hospital series, and see Table XIX.

TABLE XIX
BONE INVOLVED IN GROUP OF 283 CONSECUTIVE
CASES OF OSTEOGENIC SARCOMA*

BONE	NUMBER OF CASES
Femur	19
upper	7
middle	93
lower	—
	119
Humerus	36
upper	4
middle	2
lower	—
	42
Tibia	26
upper	5
middle	—
	31
Pelvic Girdle	31
Scapula	10
Fibula	—
upper	10
middle	1
lower	2
	13
Rib	14
Sternum	3
Vertebra	2
Os Calcis	4
Metatarsal	4
Phalanx (finger)	1
Clavicle	2
Radius	—
upper	3
lower	3
	6
Ulna (lower)	1
	—
Total	283

* From Memorial Hospital series, 1917-1940 inclusive

INCIDENCE

It has been estimated that bone sarcoma occurs in one out of every 100,000 persons in the United States. Platt gives the figure as one in every 75,000 inhabitants of Great Britain. Assuming that approximately 85 per cent are of the osteogenic type, this would indicate an incidence of one in 117,000. Based on a population of 134 million, it is estimated that there are between 1100 and 1200 cases in this country at any given time.

SEX

Males are more frequently affected than females; the series previously referred to showed 100 males to 60 females. No explanation of this dis-

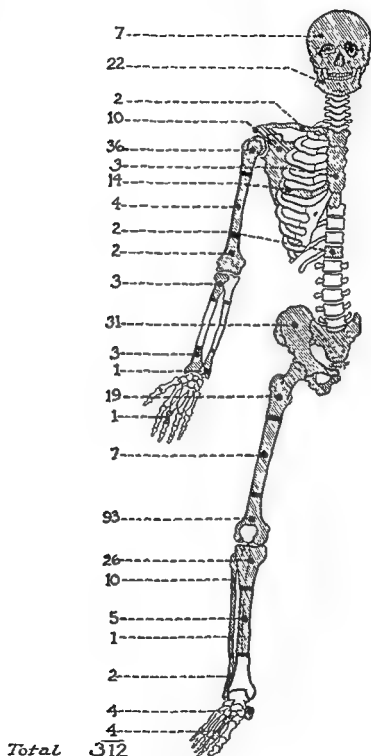


FIG. 130. Distribution of 312 cases of osteogenic sarcoma. (In this figure chondrosarcoma is included.)

crepancy has even been offered. It is possible that trauma may be an important factor since injuries to the growing ends of long bones may be looked for more often in males than in females (see Table XIX).

TABLE XX
AGE INCIDENCE OF OSTEOGENIC SARCOMA*

AGE	TOTAL	DEAD OF DISEASE	5-YEAR SURVIVALS	PERCENTAGE OF 5-YEAR SURVIVALS
1-10 years	8	7	1	12.5
11-20 years	57	45	12	21.1
21-30 years	25	17	8	32.0
31-40 years	26	18	8	30.8
41-50 years	19	17	2	10.5
51-60 years	13	12	1	7.7
61-70 years	11	8	3	27.3
71-75 years	1	1	0	0.0
	160	125	35	21.9

* Memorial Hospital series, 1917-1935.

AGE

Though essentially an affection of youth, osteogenic sarcoma can occur at any age. Table XX shows the age incidence by decades and indicates the extremely lethal character of the disease in children under 10 years of age and the more favorable outlook for those from 21 to 40 years of age.

CLINICAL FEATURES

In the various forms of this disease there is a wide variation in the rate of growth, the degree of bone destruction and the severity of symptoms. In general, cases of sudden onset with severe symptoms and rapid increase in size are highly malignant. They have a poor outlook regardless of the mode of treatment adopted. On the other hand, those of protracted onset associated with mild or moderate pain and a relatively slow rate of growth are usually much less malignant.

Sometimes the patient dates his trouble from a blow or other injury. This may have significance as a causative factor, but it is more probable that the slight injury called the patient's attention to a preexisting tumor. Ewing has called this "traumatic determinism."

When examining a patient with a suspected osteogenic sarcoma of a long bone it is important to palpate the groin or axilla. The presence of a discrete oval or round mass in these regions nearly always indicates a venous mural tumor mass; such cases have almost without exception gone on to a rapid termination with pulmonary metastasis. Less often one may note a palpable mass in the iliac fossa which means extension along the vein from Scarpa's triangle into the pelvis. One should be aware of the existence or absence of these masses before undertaking any treatment. Amputation in the presence of such a mass must be regarded as purely palliative.

Lymph-node involvement in osteogenic sarcoma is rare. Phemister, in a personal communication, states that he has seen it on several occasions.

One case in particular he regards as established beyond a doubt by microscopic evidence. This is the only acceptable criterion. Several indisputable cases have been observed at Memorial Hospital. In most instances localized oval masses in the groin are venous implants.

If, when first examined, the patient presents roentgenographic evidence of pulmonary metastasis and the primary tumor is situated in an operable location, the question arises whether to perform either an amputation or a resection in view of the hopeless outlook. Amputation has, in many instances, been of value in affording comfort to the patient, prolonging his life, and improving his morale. Two factors must be taken into consideration: (1) If the tumor is a rapidly growing one and the metastases are extensive, the period of survival will obviously be short, perhaps too short to make amputation worthwhile, but if the anticipated period of survival is six or more months there is more justification for radical procedure. (2) The probable psychologic effect of amputation on the patient and his family must be taken into consideration. Much depends upon the manner in which the situation is explained to them. Individuals differ in their reaction to a proposed amputation. Certain cases with slowly growing inoperable tumors of the pelvic girdle and of the upper femur should have the benefit of a chordotomy. In more than a dozen cases personally observed this palliative operation has produced gratifying results. It may be expected to abolish or largely eliminate pain which is due to the primary tumor. This palliative measure is indicated more often in slowly growing tumors where a prolonged period of suffering is anticipated. It is questionable whether it should be performed in cases where the expectancy of life is only a few months. Recently wider use has been made of hemipelvectomy for these tumors.

SYMPTOMS

Pain in the affected bone is the earliest symptom. At first it is insidious, of a fleeting, transitory nature, but it rapidly becomes persistent and more severe, generally robbing the patient of his sleep, and finally developing into a deep, boring pain, excruciating and almost intolerable.

Swelling may be absent, or only very slight at first, but after a variable period of time it takes on the shape of a diffuse, often eccentric, fusiform tumor of the underlying bone. As it increases in size its outline and consistence are more easily defined. There is a variation in the degree of hardness of the tumor; it may be stony in the sclerosing variety or elastic as in the osteolytic type. Pulsation is extremely rare. So-called eggshell crackling is almost never observed. The skin over the tumor later becomes stretched and is smooth and shiny in appearance. Superficial veins are frequently dilated, and their marked prominence may indicate that the deep veins of

the extremity have been plugged by tumor-tissue thrombi. Their presence is therefore an ominous sign.

Disability is variable. Early in the course of the disease it may be minimal; usually, however, some restriction of full motion is observed at the neighboring joint. A slight limp is often present. The careful observer will note that the articulation itself is not involved early in the disease; indeed, actual invasion of the joint is unusual even in far-advanced stages.

Cough, pain in the chest, and hemoptysis are late symptoms of pulmonary metastasis. Actually, however, dissemination to the lungs occurs as a singularly symptomless affair in most cases and can be detected early only on the roentgenograms. It is obvious that chest films in both postero-anterior and lateral projections should be made at the initial examination before radical surgery is undertaken, and they should be repeated at intervals during the subsequent follow-up.

PHYSICAL EXAMINATION, ROENTGENOGRAPHIC AND LABORATORY STUDIES

The investigation of a given case should include a careful physical examination as well as roentgenographic and laboratory studies (see Chap. 3, p. 22).

A biopsy, either surgical or aspiration, should always be performed before a decision regarding treatment is reached.

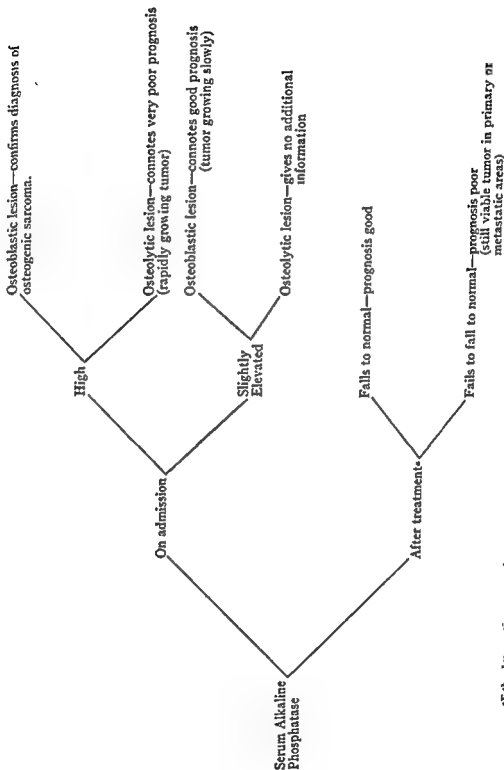
VALUE OF PHOSPHATASE DETERMINATION

Information gained from phosphatase studies in relation to the activity of a given osteogenic sarcoma may be of value. The following points, which are summed up in Table XXI, are the main diagnostic guides:

1. In an osteoblastic tumor with a high serum alkaline phosphatase, the latter merely confirms the roentgenographic diagnosis of osteogenic sarcoma.
2. In an osteolytic lesion, a high serum alkaline phosphatase indicates a rapidly growing tumor (rate too rapid to calcify), and thus an extremely unfavorable prognosis.
3. In an osteoblastic tumor with only a slightly elevated serum alkaline phosphatase, the prognosis is more favorable for it indicates a more slowly growing tumor or one whose phosphatase is not leaking into the serum.
4. In an osteolytic tumor with only a slightly elevated serum alkaline phosphatase, this determination is of no aid in establishing a diagnosis.
5. If the phosphatase is high before treatment and following either roentgen radiation or amputation it fails to decline to normal, the outlook is bad because it indicates either residual viable disease or metastasis.
6. In phosphatase-producing osteogenic sarcoma, the phosphatase activity is nearly always reduced greatly by a calculated tissue dose of

TABLE XXI

SERUM ALKALINE PHOSPHATASE IN DIAGNOSIS AND PROGNOSIS OF OSTEOGENIC SARCOMA



*Either by resection amputation, or radiation therapy.

4000 r or more; in cases receiving a smaller dose, the inactivation is irregular and incomplete.

7. If the serum phosphatase is high the tissue phosphatase is also high, but if the serum phosphatase is normal the tissue phosphatase may or may not be elevated.

8. Where phosphatase is high before amputation but falls to normal levels following operation and remains normal for a period but then rises again this is almost certain evidence of metastasis. Often this test will indicate the presence of pulmonary spread months before foci are demonstrable on chest films.

DIFFERENTIAL DIAGNOSIS

While the diagnosis of osteogenic sarcoma may not be difficult to make in typical cases, especially when seen in a relatively advanced stage, there are many instances in which the condition is mistaken for other pathologic processes. Early diagnosis is not often arrived at, although it is essential if end-results are to show improvement.

The wide use of early roentgenographic examination and chemical studies of the serum calcium, phosphorus, and phosphatase will clear up some of these mistakes; in others, recourse to histologic examination will be necessary before arriving at an accurate diagnosis.

Among the conditions which may simulate osteogenic sarcoma, the following are considered important:

1. *Endothelioma*

This tumor frequently has its origin in the metaphyseal region of a long bone and produces the triad of pain, swelling, and disturbed function. It does not produce tumor bone, and radiating striae at right angles to the shaft are not seen, yet it is often associated with reactive bone; however, the lamellar appearance parallel to the long axis and the tendency to involve a greater extent of the shaft are features that should help to distinguish it from osteogenic sarcoma. Of great importance is the age incidence of endothelioma; it is rare in persons past the age of 30, while osteogenic sarcoma may occur at any age. In many instances these conditions cannot be distinguished with certainty except by microscopic study of sections.

2. *Giant Cell Tumor*

This condition only infrequently resembles osteogenic sarcoma. When confusion arises, it is in determining whether a central area of bone destruction in the epiphyseal region is due to an osteolytic medullary fibrosarcoma, a central non-bone-forming osteogenic sarcoma, or an aggressive giant cell tumor. Malignant giant cell tumor, though rare, may afford a

most difficult problem in view of its resemblance to osteolytic osteogenic sarcoma (see pp. 45 and 184-185).

3. *Reticulum Cell Sarcoma*

This rare tumor much more closely resembles endothelioma, both roentgenographically and microscopically. However, like endothelioma, there are instances in which it may closely simulate osteogenic sarcoma, and histologic proof is the final deciding factor. Both this tumor and endothelioma are radiosensitive, and the character of the response to therapeutic X-ray may therefore be strong corroborative evidence.

4. *Inflammatory Conditions of Bone*

These conditions are more often confused with endothelioma than with osteogenic sarcoma. However, sclerosing osteitis (Garré, Henderson) and a tumorlike lesion described by Jaffe as "osteoid osteoma" may resemble early sclerosing forms of osteogenic sarcoma. The former presents an intact cortical line, and the latter a central, partially translucent spot or "nidus." Expert roentgenologic opinion can usually make these differential diagnoses.

5. *Post-traumatic Conditions*

Such diseases as ossifying hematoma (*myositis ossificans*) may occasionally pose very difficult decisions. The microscopic picture of ossifying hematoma may resemble osteogenic sarcoma so closely that a distinction may be impossible, and great weight must be given in such cases to the stereoscopic X-ray appearance. In subperiosteal ossification or in ossifying hematoma there is no break in the continuity of the cortex, whose surface presents an intact outline, whereas in osteogenic sarcoma there is destruction of the cortical bone. This information may be lacking on a single exposure but is clearly afforded from stereoscopic views. Fortunately, in several difficult decisions, amputation was withheld in cases which later were proved not to have been osteogenic sarcoma. There have been cases in the past in which needless sacrifice of a limb has resulted from failure to interpret correctly the benign character of these lesions.

6. *Metastatic Cancer*

This can simulate osteogenic sarcoma, especially when only one area is demonstrable; however, as middle adult life is reached, the latter condition is less common. On the basis of probability, the likelihood of a suspected osteolytic lesion being metastatic rather than primary in a person over 40 years of age is better than two to one. In patients over 30, a complete skeletal roentgenographic examination is indicated; if more than one area of bone is involved, the strongest likelihood exists that their origin is

tumors, where resection is a wholly justifiable procedure, there are seldom any other locations where it has been followed by any degree of success. The Bone Sarcoma Registry records only two five-year survivals. One of these occurred in a case of multiple exostoses, one of which developed sarcomatous changes, was excised, and radium employed later. In tumors developing from cartilage, there is somewhat greater opportunity to practice conservative resection (see Chap. 50, p. 490).

AMPUTATION

The most difficult decision to make is whether or not to advise amputation in rapidly growing, highly malignant osteogenic sarcomas in young children, especially those under the age of 10 years. This age group furnishes a pathetically small percentage of survivals after amputation; in fact, our records show only one such case, and in this instance we deferred amputation for seven months and in the interval gave two courses of heavy high-voltage roentgen therapy.

In view of our experience and that of the Bone Sarcoma Registry, we feel so pessimistic about early amputation in young patients that we have advised it less often of late and only with reluctance, even though realizing no other form of treatment offered the least prospect of cure.

The reason for failure to check the disease in this age group has seemed clear. The majority of these patients have a rapidly-growing, highly lethal form of sarcoma which is characterized almost invariably by its proclivity to metastasize early; hence, it is the rule to find that soon after amputation the chest films, previously negative, have become positive for metastases. Until we can establish the diagnosis in these children sooner and amputate in an earlier phase of the disease, we cannot expect to improve our results by amputation.

Principles and Indications

Rarely, if ever, should amputation be prescribed on the basis of roentgenographic evidence alone.

During the diagnostic survey the affected part should be kept at rest. If the sarcoma involves the upper extremity, a sling or splint should be worn; if it involves the lower extremity, crutches should be used; and if it is in the trunk, the patient should be kept in bed. These measures are taken in an attempt to avoid early dissemination of the disease.

In general, amputation is indicated: (1) as an attempt at permanent cure, or (2) as a palliative measure for relief of pain and to rid the patient of a cumbersome, useless extremity, where fungation and infection are impending, even though there is evidence that metastasis has already taken place (see Fig. 131).

For the first objective the indications are more clear-cut, but where the

procedure is obviously one of palliation only, the life expectancy *with* and *without* amputation must be considered. If this is short, then amputation probably, should not be undertaken. However, in many instances the relief



FIG. 131. A, Osteogenic sarcoma of upper humerus. Extension in pectoral region makes it a case of doubtful operability. B, X-ray appearance of the same case.

from pain and the psychologic effect of ridding the patient of an offending member justify the procedure.

In general amputation should be performed proximal to the affected bone rather than through it. If on clinical and roentgenographic examination the tumor appears to be confined to the distal end of the femur, one may make an exception and amputate at the junction of the upper fourth with the lower three-fourths of the shaft or just distal to the lesser trochanter.

However, with improved prostheses for hip disarticulation and even for hemipelvectomy it seems probable that the surgeon may in the future be less concerned with the need for preserving part of the femur.

In the lower extremity, amputation through a joint is undesirable because it renders difficult an adequate prosthesis; also the pressure of weight-bearing is poorly tolerated. Hence, amputations through the ankle or knee are not recommended and have been largely abandoned.



FIG. 132. Osteogenic sarcoma of femur. Amputation upper third thigh. Eighteen months later recurrence in stump requiring hip joint disarticulation, followed by survival for nine years without evidence of further recurrence or metastasis.

In order to ascertain what risk is involved in an amputation through the affected bone rather than proximal to it a survey was made of 40 consecutive cases in which this procedure was adopted. In 39 cases the lesion involved the lower femur and in 1, the lower fibula. It was found that a stump recurrence occurred twice, or in 5 per cent, of the cases but in 1 of these a secondary hip disarticulation was followed by a five-year survival. Hence it can be fairly assumed that a hip joint disarticulation was avoided in 39 cases, while there was only 1 patient in which such a procedure would possibly have succeeded (see Fig. 132).

The five-year survival rate in these 40 cases was 14, or 35 per cent, which is slightly above the figure for the 89

selected amputations reported by Pool and Coley. An analysis shows that 15 of these patients dying of sarcoma and 5 others living with metastases had stumps free of recurrence.

The above figures ought to convince us that with careful selection of cases, in osteogenic sarcoma of the lower femur it should be possible in most instances to avoid hip joint disarticulation with very little risk of stump recurrence.

While the argument for adopting a similar policy in osteogenic sarcoma of the bones of the lower leg in the hope of saving the knee is less cogent, it is quite probable that such conservatism is safe. However, the lower end of the leg bones are infrequently affected and this decision therefore seldom has to be made.

An ideal stump should have an adequate coverage of soft parts, be free from nerve pressure, possess good blood supply, afford efficient leverage and be easily adapted for the fitting of a prosthesis. The importance of these factors should be kept in mind when amputating for osteogenic sarcoma. It is possible that at times the operator may have to sacrifice some

one of them for the most important consideration of all, i.e., adequate removal of a limb which is the site of a lethal tumor.

Tables XXII and XXIII summarize experiences in the site and results of amputation and other forms of therapy. From these tables it would seem

TABLE XXII

METHODS OF TREATMENT IN FIFTY-FIVE CASES OF OSTEOGENIC SARCOMA (INCLUDING CHONDROSARCOMA) WITH FIVE-YEAR SURVIVALS^a

AMPUTATION	Alone	11	50
	With preoperative radiation	10	
	With postoperative toxins	10	
	With both toxins and radiation	19	
RESECTION OR EXCISION	Alone	1	3
	With preoperative radiation	1	
	With radiation ^b and toxins	1	
RADIATION WITHOUT SURGERY	Alone ^b	1	2
	With toxins	1	
			55

^a Memorial Hospital series. Five of the 55 cases died of sarcoma after five years.

^b Radium needles used.

TABLE XXIII
SITE OF AMPUTATION

	NUMBER OF CASES	FAILURES	5-YEAR SURVIVALS
Submitted to amputation	92		
Suitable for end-result study	89		
Amputated through bone involved	42	27 (65%)	15 (35%)
Amputated through joint proximal to bone involved	19	15 (78%)	4 (21%)
Amputated through bone proximal to bone involved	28	18 (65%)	10 (36%)
Totals	89	60 (66%)	29 (33%)

* Includes interscapulothoracic disarticulation.

apparent that amputation is of value in osteogenic sarcoma and, furthermore, amputation through the bone which is the site of an osteogenic sarcoma is justified. While admitting that in most instances it is desirable not to transect the affected bone, we are strongly of the opinion that a hip joint disarticulation should not be recommended for every osteogenic sarcoma of the lower end of the femur. If this had been done in our series a significant number of patients would have been consigned to the use of crutches who have been able to get along with a satisfactory artificial limb. In our experience this is a matter of great economic and psychologic importance. Moreover, at this point it should be stated that even with hip joint disarticulation osteogenic sarcoma of the middle or upper third of the femur almost invariably has a fatal termination.

Sequelae of Amputation

Recurrence in the stump or adjacent groin or axilla (tumor thrombus) is one of the most distressing sequelae of amputation for osteogenic sarcoma. It is unusual when marrow smears and gross inspection at the level of saw-cut fail to demonstrate upward extension of the sarcoma. It generally indicates that the tumor was of a type prone to fatal termination; this, perhaps, because of the inherent growth characteristics of the particular tumor or because of delay in carrying out surgical therapy. Where the original amputation was performed through the thigh or arm, the treatment of the recognized stump recurrence may be regarded as merely palliative. Disregard of the rule, *never to amputate through the affected bone*, has resulted in an occasional stump recurrence.

While the adoption of the present method of dealing with the major nerve trunks has almost entirely eliminated painful amputation stumps, persistent and severe causalgias are occasionally encountered. These, in our experience, have been relieved by operation for removal of neuromas.

Contracture most often arises in amputation below the knee. This can usually be avoided: first, by splinting the stump in extension at the time of operation; second, by early mobilization carried out voluntarily by the patient soon after the first dressing, and finally, by avoiding a skin flap so tight that the patient has to hold the knee flexed in order to minimize the tension.

RADIATION THERAPY

In general, osteogenic sarcoma is extremely radioresistant and the results obtained solely by irradiation have not compared favorably with those following early amputation; thus it is the practice to reserve radiation for inoperable sarcoma or for operable sarcomas in which amputation has been refused. Preoperative radiation in young children, however, seems justified since there are exceedingly few recorded five-year survivals under the age of 10 or 12 years who were treated by radical surgery alone or by radiation alone. A thorough course of radiation followed by amputation (if consent can be obtained) is worthy of trial in young patients (see Fig. 133).

One of the largest series of unselected cases (70) of osteogenic sarcoma treated by radiation without amputation ever reported from a single institution was that published by the author in 1935. These cases were compiled from a total of 200 treated at Memorial Hospital during the decade from January 1, 1923, to January 1, 1933. During this period no single standardized technic of radiation therapy was used. Both roentgen-rays and radium pack were employed either separately or combined. In 24 of the 70 cases a massive dose, in 25 fractional doses, was given, while in 21 cases the technic varied so that it could not be classified as either massive or fractional.



FIG. 133. Osteogenic sarcoma. Note skin discoloration resulting from heavy dosage of high-voltage X-ray; also fusiform enlargement with obliteration of surface landmarks. Outline of X-ray therapy portals can be made out.

At the time of the report 64 of the 70 patients were dead and only 1 of the 11 living patients had survived for five years.

Four of the 11 living patients had fibrosarcoma, a fifth had a secondary sarcomatous development on a cystic osteitis which we now suspect was fibrous dysplasia. The diagnosis in the remaining case, based on roentgenographic evidence without microscopic confirmation, was that of sclerosing osteogenic sarcoma.

From this study we were convinced, as were probably other investigators, that roentgen therapy as applied during this period yielded such discouraging results that it was scarcely justified as an alternative to early amputation for the treatment of operable osteogenic sarcoma. In view of a more recent study by Woodard and the author of the results of high-voltage roentgen therapy in respect to estimated dosage *actually delivered to the tumor* as determined by its effect on the clinical setting, the levels of serum alkaline phosphatase, the histologic evidence of destruction of tumor cells, and the subsequent course of the primary growth, we now realize that many of the cases included in the foregoing series were given insufficient treatment to control the local disease. This study also convinced us that it was generally impossible to deliver adequate dosage and yet preserve a useful limb (see Chap. 56, p. 548).

There is a type of osteogenic sarcoma usually termed *periosteal fibrosarcoma* which lends itself to adequate treatment by combined interstitial and external radiation. One such case occurring in the upper arm, treated by this method, has remained well for more than ten years (Bone Sarcoma Registry, case 1453).

Methods of Radiation

When radiation is employed purely for its palliative effect, fairly large doses are usually given through each of the available portals in a single cycle. Where there is some prospect of more than temporary relief, small daily doses through all available portals in rotation are preferable. This is the method advocated for children, to be followed later by amputation if consent can be obtained.

For a suggested *method of outlining radiation of a bone tumor by fractional doses* see page 542.

Where a heavy dose of roentgen-rays has been delivered by the *fractional-dose* technic, care must be taken about repeating it lest grave damage result to the skin and soft parts (see Fig. 134). The size of the portal is important. When large portals are used, the total dosage per portal must be less. It is self-evident that no matter what technic is employed, it should be under the close personal supervision of a competent roentgenologist. It seems best to give maximal doses in a single course rather than to repeat in a second course at a later date (see Fig. 135).

Interstitial Radiation

Certain conditions must be fulfilled before interstitial radiation can be employed successfully:

1. The tumor must be mainly extra-osseous.
2. It must be small in size. It is not feasible to attempt this method with very bulky tumors. Any tumor having an estimated volume of more than 500 cc. is probably too extensive for successful interstitial radiation
3. It must be situated far enough from vital structures (sciatic nerve, femoral or axillary vessels, etc.) to ensure them against serious damage from intense radiation.

As previously mentioned, there are only exceptional cases when this method may be even remotely applicable.

Treatment by Radioactive Phosphorus

Several years ago various types of primary malignant bone tumors were treated by intravenous or oral administration of radioactive substances, chiefly radioactive phosphorus. It was found that phosphatase-producing osteogenic sarcomas showed a high differential uptake of radioactive phosphorus when compared with normal bone or other body tissues. The maximum radiation dose which could be administered to the tumor from this source without imperiling the health of the patient did not exceed 1000 equivalent roentgens, and was usually considerably less. In a radioresistant tumor, such as osteogenic sarcoma, this dose is insufficient to cause much improvement. The uptake of radioactive phosphorus by Ewing's tumor is much less than by osteogenic sarcoma so that, although this tumor is radio-sensitive, therapeutically effective doses of radiation cannot be administered by means of radioactive phosphorus.

PULMONARY METASTASES

Treatment by Radiation

Notwithstanding an occasional exception, pulmonary metastases from osteogenic sarcoma are not benefited by external radiation (see Fig. 136). It has been found that the unpleasant constitutional effect as well as the effect on the hemopoietic system far outweigh the scant benefit obtained, i.e., slight temporary growth-restraint. This is in marked contrast to the striking palliative effect of radiation of the chest for metastatic endothelioma of bone. If it has been decided to try radiation, small portals should be used wherever possible, thus permitting the employment of larger doses without skin damage. Often three small portals (anterior, posterior, and lateral) can be used to deliver to a single pulmonary metastasis the maximum effective dose of radiation. Where both lungs are involved with many

small or several large metastatic nodules the use of any form of radiation is a questionable procedure. At Memorial Hospital we have almost entirely abandoned it.



FIG. 136. Pulmonary metastases from osteogenic sarcoma.

Treatment by Surgery

Up to the present time there is no record of any case of pulmonary metastases from osteogenic sarcoma in which lobectomy has been followed by five-year survival; furthermore, few instances occur in which such a procedure could be regarded as justified. Yet because not all osteogenic sarcomas terminate with multiple metastases, it is possible that in the future an exceptional success may be achieved by lobectomy in a solitary slowly developing metastasis situated well out in the parenchyma of a lobe. The possibility of such an outcome is too uncertain to be encouraging. The reader is referred to the article by Alexander and Haight (see Bibliography, p. 345).

We have under observation a patient in whom, more than five years after amputation for chondrosarcoma of the femur, a single, small pulmonary metastasis was present. A resection of the area of lung containing the metastatic focus was done recently and one cannot yet be assured of the ultimate result. However, this particular case seems exceptional and we are hopeful of a permanent cure. There seems every reason to believe that in selected cases this procedure deserves further trial.

Treatment with Mixed Toxins of Erysipelas and Bacillus Prodigiosus (Coley's Toxins)

For many years it was our policy to give injections of toxins according

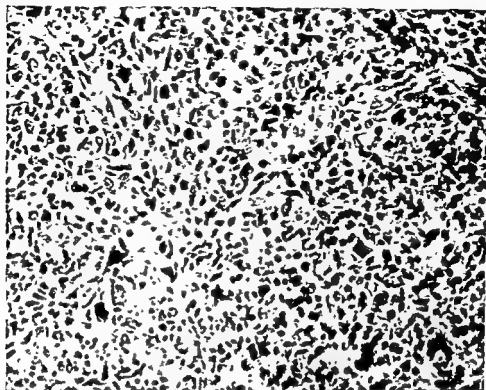


FIG. 137. Microphotograph of osteogenic sarcoma. A very cellular oval and polygonal cell tumor with moderate numbers of hyperchromatic giant cells. Tumor entirely osteolytic.

to the technic of William B. Coley to patients after amputation for osteogenic sarcoma. This was done on the theory that minute foci of pulmonary metastases were possibly prevented from becoming established. Statistics, however, fail to indicate that the survival rate is increased in those cases receiving toxin treatment after amputation as compared with those treated by amputation alone. We have personally observed no instance of osteogenic sarcoma where noteworthy regression was obtained either in the primary tumor or in demonstrable pulmonary metastasis by the use of the toxins. Recently we have abandoned its use and no longer feel justified in recommending it in this disease even as a prophylactic measure after amputation or resection where no evidence of pulmonary metastasis is demonstrable on chest films (see p. 566).

PROGNOSIS

The most important single factor in the outlook of a given case is the histologic character of the tissue composing the tumor, i.e., its grading. Low-grade tumors yield more than twice as high a percentage of five-year survivals (see Figs. 137-141). There is no appreciable difference between

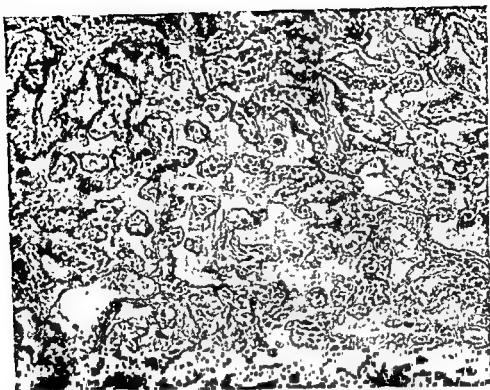


FIG. 138. Microphotograph of osteogenic sarcoma, sclerosing type. Section shows dense mosaic of atypical bone trabeculae. In the interstices are tumor cells lining the edges of bone trabeculae. This section is from an area of intermediate density. Other areas of this tumor showed solid coalescence of bone trabeculae with the formation of ivory-like osseous tissue.

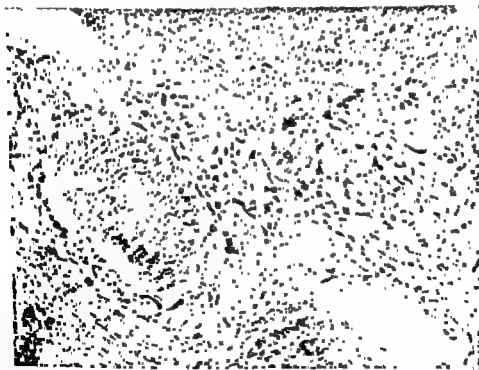


FIG. 139. Microphotograph of osteogenic sarcoma, rare telangiectatic type. Blood lacunae in some areas lined by tumor cells, in other areas by thin endothelium. Much hemorrhage within substance of tumor. Tumor cells in rather loose arrangement and principally spindle and stellate in outline.

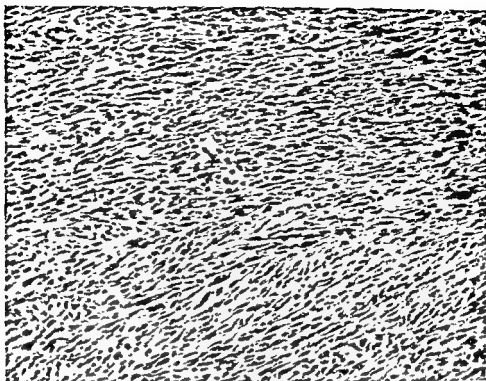


FIG. 140. Microphotograph of osteogenic sarcoma. A relatively favorable type composed of bundles of elongated spindle cells. Usually referred to as fibrosarcoma of bone. These tumors are predominantly periosteal but may be medullary.

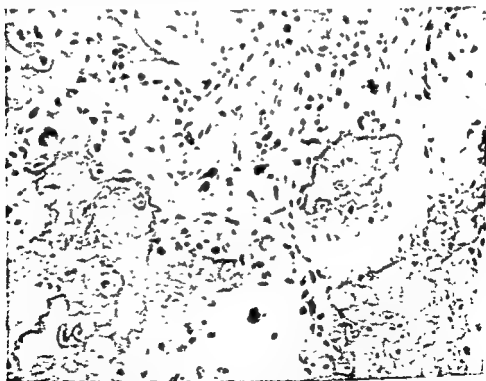


FIG. 141. Microphotograph of osteogenic sarcoma. Tumor cells of pleomorphic appearance forming osteoid and atypical bone trabeculae.

the average- and the high-grade survival rate in the Memorial Hospital series:

		FIVE-YEAR SURVIVALS
Low grade of malignancy	36	40%
Average grade of malignancy	98	16%
High grade of malignancy	26	15%

Delay in the treatment of this disease unquestionably affects the prognosis. In a detailed study of cases from the Bone Sarcoma Registry, Ferguson found that when the cases were separated into groups based on the period of delay between the patient's first symptoms and the amputation, the survival rate was directly proportional to the delay. In other words, where the interval was less than three months the survival rate was extremely low; it improved with each six-months' interval until those amputated a year or more after onset of symptoms had a very good outlook. These facts brought out by Ferguson are indisputable. Our own figures for the 160 cases alluded to in this chapter led to essentially the same conclusions. However, we strongly differ with Ferguson's interpretation that *the delay in amputating was in any way responsible for the better prognosis*. It seems far more probable that the slowly growing tumors caused less alarming symptoms and that radical surgery was thus deferred longer, while the highly malignant, rapidly growing tumors received more prompt attention and were amputated earlier. It does not appear reasonable that once the diagnosis has been established there should be any avoidable delay in amputating. However, if permission cannot be obtained at once, it is safer to institute heavy roentgen therapy during the period in which efforts are made to obtain consent for it is believed that this therapy does minimize the hazards of delay. The accompanying tables (XXIV and XXV)

TABLE XXIV

METHODS OF TREATMENT OF ONE HUNDRED AND FORTY-FOUR CASES OF OSTEOGENIC SARCOMA*

	TOTAL	DEAD OF DISEASE	FIVE-YEAR SURVIVAL
Amputation only	17	12	5
Amputation and radiation	15	12	3
"	41	27	14
"	4	1	3
"	2	1	1
"	6	4	2
"	4	3	1
Resection only	17	15	2
Radiation only	35	32	3
Curettage and radiation	3	2	1
	141	109	35

* Of the entire group of 160 cases, 16 were unsuitable for this analysis: three died following operation elsewhere; nine had only palliative treatment following metastases, and four were too far advanced for treatment. This table includes chondrosarcomas.

NEOPLASMS OF BONE

TABLE XXV
ANALYSIS OF RESULTS IN OSTEOGENIC SARCOMA*

	1917-1934	1935-1940	TOTAL
Clinical diagnosis	217	125	342
Without histologic verification	53	16	69
With histologic verification	164	109	273
a. <i>Indeterminate Group:</i>			
1. Dead of other cause in less than five years without recurrence	3	3	6
2. Lost to follow-up with recurrence	1	1	2
	<u>4</u>	<u>4</u>	<u>8</u>
b. <i>Determinate Group</i>			
1. Failures:			
(a) Dead of sarcoma	121	72	193
(b) Lost to follow-up with disease	4	7	11
(c) Died of other cause but with disease	0	1	1
(d) Postoperative deaths	0	2	2
	<u>125</u>	<u>82</u>	<u>207</u>
2. Successes:			
(a) Free of disease 5 or more years after treatment	35	23	58
Five-year survival rate (determinate group)	21.8%	21.9%	21.9%

* Memorial Hospital series, 1917-1940 inclusive. This table includes chondrosarcomas.

show the results in two series. Table XXVI summarizes the five-year survivals.

UNUSUAL FORMS OF OSTEOGENIC SARCOMA

Several unusual manifestations of osteogenic sarcoma should be briefly considered.

Sarcoma developing on the basis of a myositis ossificans (or calcifying hematoma) has been observed. This is unquestionably an extremely rare condition and in the vast majority of cases of myositis ossificans the histologic resemblance to osteogenic sarcoma should not lead to a hasty conclusion that the condition is malignant and hence requires amputation. It calls for the exercise of great caution to avoid such a tragic mistake.

Myositis ossificans tends to improve as time passes and osteogenic sarcoma grows steadily worse. Bone is never destroyed in myositis ossificans and irregular destruction of bone already laid down is suggestive of sarcoma.

Some cases of Paget's disease (10 to 12 per cent) with symptoms sufficiently severe to cause the patients to ask for medical advice, develop a type of malignant bone tumor that has been termed *osteogenic sarcoma*. It is probable that many mild cases of Paget's disease are never recognized and seldom give rise to malignant changes (see Chap. 71, p. 663).

OSTEOPETROSIS (ALBERS-SCHONBERG DISEASE)

Kerr, in 1936, recorded the only example of osteogenic sarcoma arising in bone already the site of changes, known as osteopetrosis or "marble bones" (Marmor Knochen). For more details see page 673.

EXTRASKELETAL OSTEOGENIC SARCOMA

Though osteogenic sarcoma unrelated to traumatic myositis or to the bony skeleton is rare, it has been fully described and is well recognized.



FIG. 142. Osteogenic sarcoma of femoral shaft.



FIG. 143. Advanced, inoperable osteogenic sarcoma.

As early as 1700 Boneti reported the finding of an osteoma in a female breast, and since then Morgagni, Astley Cooper, and Johannes Müller have described others. In 1937, Ross collected 8 recorded examples of osteogenic sarcoma in the mammary gland.

Wilson (1941) found but 30 instances of extraskeletal osteogenic sarcoma reported in the literature and added 7 more from the Bone Sarcoma Registry and the Departments of Surgery and Pathology of the University of Chicago. Parsons and Henthorne in 1944 reported an additional case. Thus it appears that less than 50 cases have been recorded.

The mammary gland and thyroid have accounted for nearly 65 per cent of these soft-tissue osteogenic sarcomas. Six occurred in the thigh, 2 in the gluteal region, and 1 each in the mesentery, kidney, abdominal wall, gall-bladder, chestwall, vastus externus muscle, gastrocnemius muscle, mediastinum, arm, and leg. The case reported by Parsons and Henthorne was the first involving the lip.

In 1944, Tremblay *et al.* described a case in the bladder and found in the literature 8 other instances of primary bladder tumors of bone or cartilage.

TABLE XXVI
SUMMARY OF FIVE-YEAR SURVIVALS OF OSTEOGENIC SARCOMA*

No.	Year	Name	Sex	Age	Bone	Surgery	Radiation	Toxins	Survival yrs.	Survival mos.	
1.	1919	B. M.	F.	35	Femur	Amputation			16	0	
2.	1922	K. F.	F.	29	Rib	Resection	X	X	24	6	
3.	1919	H. S.	M.	19	Femur	Amputation	X	X	19	0	
4.	1920	L. O'N.	F.	31	Humerus	Amputation	X		11	0	
5.	1921	L. R.	M.	12	Humerus	Disarticulation	X		11	9	
6.	1921	J. C.	M.	12	Tibia	Amputation	X		24	6	
7.	1921	J. D.	F.	21	Femur	Amputation			14	0	
8.	1923	R. M.	F.	8	Tibia	2 resections & amputation	X		12	8	
9.	1925	C. C.	F.	34	Humerus	Disarticulation	X		20	8	
10.	1927	H. N.	M.	16	Fibula	2 resections & amputation	X		18	3	
11.	1927	L. T.	F.	63	Femur	Amputation	X		5	3	
12.	1928	T. P.	F.	37	Femur	Amputation	X		17	8	
13.	1932	J. M.	M.	38	Tibia	Resection & radon needles	X		13	11	
14.	1929	L. S.	M.	47	Tibia	Resection & amputation	X		12	3	
15.	1929	G. M.	M.	16	Tibia	Amputation	X		14	4	
16.	1930	G. R.	F.	36	Humerus		Radon needles			4	4
17.	1929	W. H.	M.	19	Femur	Amputation			9	2	
18.	1930	L. W.	F.	34	Metatarsal	Resection & amputation			16	5	
19.	1929	T. S.	F.	19	Tibia	Amputation			15	6	
20.	1931	D. W.	F.	17	Femur	Amputation	X		16	10	
21.	1930	S. K.	M.	62	Femur	Amputation	X		14	2	
22.	1930	S. G.	M.	59	Ilium	Amputation	X		9	7	
23.	1931	A. S.	F.	24	Ulna	Amputation	X		7	0	
24.	1931	J. S.	M.	65	Metatarsal -	Amputation			15	5	
25.	1931	H. F.	M.	21	Tibia	Amputation	X		14	7	
26.	1932	B. S.	M.	43	Femur	Amputation	X		14	8	
27.	1932	D. B. McC. F.	F.	15	Os calcis	Amputation		X	11	9	
								X	13	6	

28.	1932	S. H. G.	M.	17	Ulna	Amputation	X	12	4
29.	1933	F. S.	M.	35	Scapula	Resection		10	0
30.	1934	L. B.	M.	29	Fibula	2 resections & amputation; partial pneumonectomy for metastases 6 yrs. later	X	5	1*
31.	1934	C. T.	F.	34	Humerus	Curettage & disarticulation		10	5
32.	1934	M. B.	F.	15	Femur	Amputation	X	12	1
33.	1934	A. L.	M.	21	Femur	Local excision & amputation	X	11	1
34.	1934	D. G.	M.	16	Femur	Amputation	X	6	3
35.	1935	E. B.	F.	6	Femur	Curettage & amputation	X	10	6
36.	1935	M. B.	M.	44	Femur	Amputation		10	10
37.	1940	E. B.	F.	16	Tibia	Amputation	X	5	0
38.	1937	H. B.	F.	38	Femur	Excision of tumor (limb saved)		9	0
39.	1936	J. B.	M.	23	Humerus	Interscapulothoracic	X	11	0
40.	1940	A. C.	M.	28	Fibula	Mid-thigh amputation	X	5	7
41.	1935	H. F.	F.	19	Scapula		X	9	7
42.	1939	C. H.	M.	39	Tibia	Low-thigh amputation		6	11
43.	1935	E. H.	F.	12	Humerus	Interscapulothoracic	X	10	4
44.	1938	M. H.	F.	14	Femur	High-thigh amputation	X	8	1
45.	1935	M. J.	F.	68	Sternum		X	7	11*
46.	1936	M. L.	F.	11	Femur	High-thigh amputation	X	9	11
47.	1939	L. L.	F.	39	Femur	Amputation		6	3*
48.	1935	W. R.	M.	23	Femur	Hip-joint disarticulation	X	5	0
49.	1936	R. R.	F.	12	Femur	High-thigh amputation		9	4
50.	1937	M. R.	M.	17	Femur	Mid-thigh amputation	X	9	0
51.	1939	D. S.	M.	15	Femur	High-thigh amputation	X	7	1
52.	1940	J. S.	M.	16	Tibia	Supracondylar	X	5	4
53.	1940	A. V.	M.	22	Humerus	Shoulder disarticulation	X	5	7*
54.	1939	H. T.	M.	26	Femur	High-thigh amputation (elsewhere)		12	2
55.	1936	M. W.	F.	26	Fibula	Amputation below knee	X	10	2
56.	1941	M. K.	F.	31	Tibia	Curettage & cauterization		5	0
57.	1941	B. M.	F.	29	Femur	Amputation, mid-thigh		6	0

* Memorial Hospital series, 1917-1941 inclusive. Table was compiled in 1947 and includes chondrosarcomas

* Paget's disease

* Patients who died of sarcoma more than five years later

They hold the view that these tumors arising near the trigone are derived from mesoblastic remnants of the wolffian body.

Two theories are advanced with regard to the mechanism by which

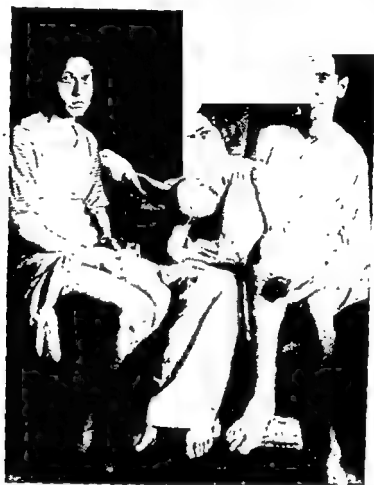


FIG 144. : Concurrent osteogenic sarcoma in a brother and two sisters (Courtesy of Dr. C. W. Roberts and Dr. C. P. Roberts.)

osteogenic sarcoma develops in soft tissue: One, upheld by Broders, attributes it to anaplasia of fibrous tissue cells to fibrosarcoma, following which the neoplastic fibroblasts differentiate into osteoblasts and are responsible for the formation of osseous tissue. The other theory, supported by Leriche and Policard, and Mallory, regards these osteosarcomas as fibrosarcomas passively ossified by the condition of their environment. Actually the distinction between these two theories is not clear. It lies in substance between those who believe that the osseous transformation of connective tissue is an interstitial and humoral process independent of cellular activity and those who believe that the osteoblasts of a tumor secrete a true osseous substance.

The following case is of interest on account of its unusual roentgenographic features and because it offered an opportunity for a conservative operation, rather than an immediate amputation:



FIG. 148. Gross specimen of osteogenic sarcoma showing invasion of vein.

CASE REPORT:

H. M., a schoolboy aged 14, was admitted to the Hospital for Special Surgery on Nov. 26, 1946. He had always been well until three months previously when

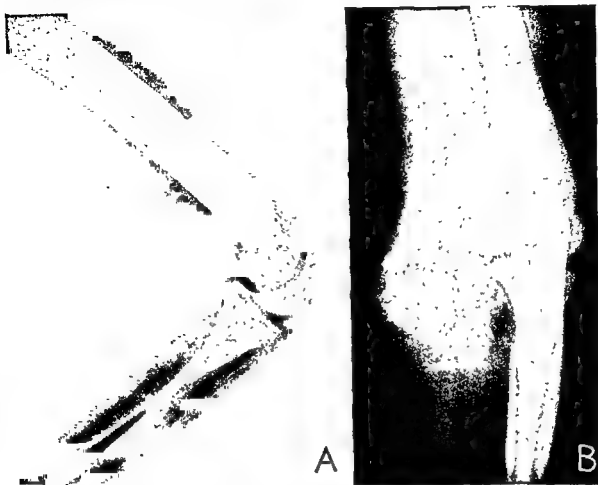


FIG. 149. Osteogenic sarcoma arising in the soft parts, not connected with bone. A, Appearance on November 5, 1946, B, three weeks later. The mass was removed and reported to be osteogenic sarcoma of low grade. The pathologist considered the prognosis excellent and did not recommend an amputation. Patient is well and without evidence of disease eighteen months later.

he complained of occasional pain and tenderness about the left elbow. While there was no definite history of injury the patient was inclined to attribute his symptoms to bruising received in football practice. Eight weeks prior to admission a swelling on the flexor surface of the elbow region was noticed. No treatment was given for four weeks, when, because of the increase in symptoms and the fact that the original clinical diagnosis had been that of inflammatory process, the family doctor administered penicillin. There was no improvement. One week later he operated with a view to incising and draining a suspected abscess—the swelling and tenderness having meanwhile increased so as to interfere with full extension of the forearm—but instead he encountered a solid tumor. A piece was removed and on microscopic examination was pronounced osteogenic sarcoma. This diagnosis was confirmed by Dr. Stewart of Memorial Hospital who considered the lesion, because of its position in the soft tissues and its non-

attachment to bone, susceptible of removal without resorting to amputation. In the week preceding the biopsy there had been marked increase in the size of the mass although it remained freely movable.



A



B

FIG. 150. A, Osteogenic sarcoma of ilium, osteolytic type. Closely resembles plasma cell myeloma or metastatic carcinoma. B, Shows continued progress of the destructive process with tendency of the head of the femur to luxate upwards into the pelvis.

Physical examination on admission was negative except for the local condition. There was a hard tumor mass on the volar aspect of the left forearm which interfered with full extension of the elbow. There was a freshly healed skin incision directly over the center of the mass.

A roentgenogram, November 27, 1946, revealed a lobulated calcareous body about 3 cm. in diameter lying near the muscles anterior and lateral to the upper extremity of the left radius. It produced a considerable degree of bulge on the anterolateral surface. There was no evidence of connection with bone (see Fig. 142).

On this date operation was performed, using a tourniquet and cyclopropane anesthesia; the tumor was removed with difficulty by sharp dissection; the radial artery had to be divided; the median nerve was exposed but was not damaged. The tumor was quite obviously situated in the muscle but could be removed by dividing the muscle fibers without apparently entering it at any point. Cotton sutures were used throughout. The postoperative course was uneventful. The radial pulse, which was lost immediately after operation, became palpable on the fourth postoperative day, and at no time were there any signs of ischemia or paralysis.

On his discharge from the hospital, December 26, 1946, the patient's arm was in excellent condition; the wound was well healed.

Report of pathological findings by Dr. M. Helpm (Pathologist of the Hospital for Special Surgery), November 12, 1946:

Macroscopic examination: Specimen: osteogenic sarcoma, left forearm.

The specimen is an ovoid-shaped tumor mass of hard consistency, about the size of a pullet's egg, obviously calcified or ossified, embedded in skeletal muscle tissue. On section the nodule is circumscribed, gray in color, firmly attached to the surrounding tissue, the cut surface having the texture of can-

cellous bone; there are soft areas in the otherwise firm tissue which is almost entirely bony throughout. The over-all dimensions of the osseous tumor nodule are 3.8 x 3 x 4 cm. The muscle tissue in which the specimen is embedded has a pale, stretched, translucent appearance; this is especially noticeable over each pole of the tumor. One surface of the specimen is covered with a layer of subcutaneous fat to which is attached a narrow strip of skin 4 cm. in length; this contains an old linear surgical scar. There is a short, pale segment of muscle belly up to 2.5 cm. wide and 1 cm. in thickness, inserted over the tumor nodule.

Microscopic examination: Sections of the tumor nodules reveal a circumscribed mass of osteogenic connective tissue surrounded by a layer of fibrous tissue blending with the perimysium and endomysium of the surrounding striated muscle in which the tumor is embedded. The muscle fibers are separated by proliferation of fibroblasts and connective tissue in which there are scattered groups of inflammatory cells similar to what has already been described.

Within the osteogenic tumor nodule there is an abundance of well-differentiated, variably-sized and shaped interconnecting bone trabeculae enclosing large osteocytes. These trabeculae lie in a stroma of loose connective tissue, the cells of which are not unusual. Many trabeculae are surrounded by osteoclasts and by osteoblasts. Some are preformed in small islands of cartilage. Other areas in the tumor are more cellular and composed of interlacing elongated spindle-shaped cells rather compactly arranged but not especially large or hyperchromatic. These cells are separated by collagen fibrils and in places there is deposition of a pale eosinophilic ground substance suggesting immature osteoid, the latter laid down by osteoblasts differentiated from the connective tissue stroma. The well-differentiated osseous portions of the tumor do not appear especially aggressive in their growth. The intertrabecular connective tissue is loose textured and not especially cellular.

Diagnosis: Circumscribed osteogenic tumor (sarcoma ?) completely embedded in skeletal muscle.

In 1928, Rhoads and Blumgart reported 2 cases from the Boston City Hospital; both had tumors in the soft tissues of the thigh, not attached to bone, which were removed and subjected to histologic study. They fulfilled all the microscopic criteria for classification as osteogenic sarcoma. At the time of their report the authors had followed 1 of the patients for two years and the other for six months; in neither had there been any evidence of a recurrence after local excision.

Broders has demonstrated that cells in tumors of this type actually possess the potentiality for differentiation from neoplastic fibrocytes to osteoblasts. Clinically these tumors behave as do osteogenic sarcomas in bone, i.e., they recur locally, tend to metastasize, and cause death.

Since examples of malignant alteration occurring in heterotopic bone have little interest for those concerned with bone tumors and other diseases

of the skeletal system, they are mentioned here only for completeness. Certain it is that they demonstrate the remarkable powers of metaplasia of connective tissue. The paper by Stewart and Binkley is recommended for those who are interested in a more detailed consideration (see Bibliography, p. 346).

OSTEOGENIC SARCOMA DEVELOPING ON BENIGN BONE LESIONS

The possibility that osteogenic sarcoma, chondrosarcoma, or fibrosarcoma may be engrafted upon a wide variety of bone lesions which are of themselves benign should always be borne in mind. Some of these are not at all uncommon, e.g., Paget's disease of bone, chondroma, and giant cell tumor. Many, however, are conditions which are of themselves relatively rare. Among these may be mentioned fibrous dysplasia, osteopetrosis, and ossifying hematoma, in all of which sarcomatous change has either been reported or observed. Stewart has seen a case in which bilateral osteogenic fibrosarcoma of the femur developed on the basis of long-existing Gaucher's disease with bone lesions typical of this condition.

One cannot escape the conviction that long-standing diseases of bone in which the normal processes of bone wear and repair are interfered with predispose to the eventual development of sarcoma. Whether the resulting tumor is osteogenic sarcoma, chondrosarcoma, or fibrosarcoma, or whether it is entirely similar to or identical with the usual sarcomas that appear in bone that is apparently normal, is a question that remains unanswered. Morphologically they may appear to be indistinguishable. Further observation and more detailed descriptions of some of these secondary sarcomas will be found in other chapters. Of these by far the most important is the malignant giant cell tumor which develops on the basis of a preexisting benign giant cell tumor (see p. 198).

OSTEOGENIC SARCOMA DEVELOPING AFTER FRACTURE

Most cases in which a fracture is regarded as the exciting factor in the later development of a sarcoma will prove on careful scrutiny to be examples of pathologic fracture. The early roentgenograms will reveal the presence of disease in the bone so slight as to escape notice on routine examination and yet definite enough to be convincing when reviewed in the light of subsequent events.

Two cases have been observed by the author in which after a most thorough study it seems impossible to deny the fact that the bone was normal at the site of the fracture and that it later became involved by an osteogenic sarcoma. Similar cases have been reported (see p. 723, Pathologic Fracture).

SARCOMA DEVELOPING IN IRRADIATED BONE

EXPERIMENTAL PRODUCTION OF BONE SARCOMA BY IRRADIATION

The effect of irradiation upon skin and its tendency to induce carcinoma as a late sequel is now a well-established fact but it is not so generally known that bone may undergo malignant change after exposure to radium or roentgen-rays.

The first reported example of experimental bone sarcoma was that of Marie, Clunet, and Raulot-Lapointe who, in 1910, observed such a case while engaged in the study of the relationship of X-ray burns and carcinoma. Lacassagne and Vinzent, in 1929, observed an osteogenic sarcoma in a rabbit's femur six and a half months after a dose of 1000 r. Schürch and Uehlinger, in 1931, recorded the development of an osteogenic sarcoma in a rabbit's jaw one and a half years following the implantation subperiosteally of a 1-microgram radium needle. In 1936, Jentzer produced sarcoma in the cranial bones of a rabbit by radium application. Osteogenic sarcoma of the rib of a rabbit was found by Ross, in 1936, to follow implantation of radon tubes in the chestwall.

Hellner, in 1937, by repeated exposures of the lower end of the femur of a rabbit to radium was able to produce a polymorphous sarcoma. Lüdin, in the same year, delivered 8000 r over a six and a half month period to a rabbit's tibia and a chondrosarcoma developed.

Daels and Biltris performed numerous experiments with radioactive substances and produced bone sarcoma in guinea pigs and fowls, while Dunlap, Aub, Evans, and Harris, in 1944, reported osteogenic sarcomas in the pelvic bones or vertebrae of 9 of a series of 13 rats who were fed 100 micrograms of radium; the interval elapsing between feeding of radium and discovery of the sarcomas averaged 365 days. In three of these tumors transplantation to other rats was successful.

REPORTS OF CLINICAL CASES OF OSTEOGENIC
SARCOMA FOLLOWING IRRADIATION

According to Hatcher the literature up to 1945 contains a report of 19 human beings with osteogenic sarcoma occurring as a sequel to therapeutic exposures of radium or roentgen-rays. The majority, or 16 of these, were treated for tuberculous arthritis. Radium was the agent used in 1 while the remaining 18 had roentgen therapy.

It is interesting to note the interval elapsing between treatment and the recognition of the sarcoma. In the 19 cases collected by Hatcher, which includes 3 personal ones, the average interval was 6.6 years.

The foregoing series does not include 11 cases which have been fully described by Martland, viz: sarcoma developing in radium dial workers following the ingestion of minute amounts of radium and allied radioactive

substances. The latter cases present an industrial hazard and are not comparable to those which developed sarcoma following administration of radium or roentgen therapy in the treatment of disease.

PERSONAL SERIES

Cahan, Woodard, Higinbotham, Stewart, and the author have recently studied a series of 11 cases at Memorial Hospital in whom osteogenic or chondrosarcoma developed in irradiated bones after a lapse of from six to twenty-two years following roentgen- or gamma-ray treatment. We concluded that while development of bone sarcoma in bone exposed to heavy doses of roentgen ray or radium is an uncommon sequel nevertheless it does occur. It may take place either in normal bone or in a benign bone tumor, and in our experience there was a latent period of from five to more than twenty years between exposure and the recognition of a frank sarcomatous alteration. It is seldom observed following moderate dosage and probably requires a tissue dose of 3000 r or more, although one case had received only 1550 r.

When a patient who has been treated by irradiation for a benign bone lesion five or more years previously returns with complaints of pain, with or without swelling, in the area so treated, immediate suspicion of malignant change should be aroused, roentgenograms should be made at once, and biopsy material obtained. In such cases aspiration biopsy is preferable to open biopsy because of the danger of incising irradiated tissues which are notoriously slow to heal.

The late development of bone sarcoma following irradiation is another reason for our belief that roentgen therapy is not ordinarily to be recommended for benign tumors of bone. While judging from the paucity of references in the literature its incidence is small, it has most serious implications when it does occur.

TREATMENT

Surgical treatment—either immediate resection or amputation—is the only acceptable method. It is unnecessary to mention the futility of further roentgen therapy.

OSTEOGENIC SARCOMA IN RADIUM POISONING

The classical paper by Martland and Humphries (1938) reports the death of 15 girls from radium-mesothorium poisoning. It describes the manner in which luminous paint used on watch dials is absorbed in minute amounts by the gastrointestinal tract and deposited in the form of insoluble sulphates in the bones and the rest of the reticulo-endothelial system. This deposition affects all the bones uniformly though it is irregularly distributed

in the bone and is often concentrated in certain areas, notably the outer layers of the cortex.

Radiation osteitis thus is constantly being caused by a continuous bombardment by the rays, chief of which in destructive effect are the alpha rays. The mesothorium component of the luminous paint is probably the more active both chemophysically and physiologically. This radiation osteitis resembles that seen in earlier cases in which external radiation was given in extremely large or often-repeated doses.

Martland and Humphries reported 2 cases in which osteogenic sarcoma complicated this form of radiation osteitis. One of these cases is complete with autopsy findings and is unquestioned, viz: the tumor which involved the right scapula followed an injury due to a fall. The interval between the patient's employment in the dial-painting plant and the onset of the sarcoma was eight years.

The author observed another case in which a sarcoma followed "radium dial poisoning" and caused the patient's death.

After the tragic death of these 15 girl workers, proper precautionary measures in the handling of luminous paints were instituted, thus making a repetition of such cases extremely unlikely.

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After the tragic death of these 15 girl workers, proper precautionary measures in the handling of luminous paints were instituted, thus making a repetition of such cases extremely unlikely.

22. CHONDROSARCOMA

THE EARLIER CLASSIFICATION OF THE BONE SARCOMA REGISTRY PLACED malignant tumors of cartilaginous origin in the same group as other forms of osteogenic sarcoma. The term "osteogenic chondrosarcoma" was often used. In 1939, largely through the influence of Ewing, the classification was revised. One of the changes adopted was the allocation to a separate category of those tumors which arise from and produce cartilage. Previously, Phemister and others had stressed their distinguishing characteristics, and Geschickter and Copeland had emphasized, perhaps to an extreme, the role of cartilage in bone sarcoma. Morton has recently reported 13 cases which he had personally observed during a twenty-year period, and 61 others from the Bone Sarcoma Registry.

In discussing this group of tumors, it is preferable to divide it into two subgroups: (1) primary chondroblastic sarcoma, and (2) secondary chondrosarcoma (myxosarcoma of Registry classification).

PRIMARY CHONDROBLASTIC SARCOMA

This lesion occurs in children and young adults, generally between the ages of 10 and 25 years (see Figs. 151 and 152). The sites of greatest frequency are the lower end of the femur, the upper end of the tibia, and the upper end of the humerus. It arises from normal cartilage in or about the epiphyseal area. Roentgenographic examination discloses a circumscribed, multilobed area of increased density within which may be seen areas of dense calcification. There is destruction which may involve both cortical and cancellous bone, but this does not usually occur early. The periosteum is elevated and often shows reactive bone at the margins of the involved area which constitutes the *Codman's triangle* previously referred to. This tumor is among the most malignant of all bone sarcomas. Like the osteogenic varieties, it is not radiosensitive although heavy exposures may cause some regression and often temporary relief of pain. Pulmonary metastasis occurs relatively early and few cases are subjected to amputation promptly enough to save life. The ability of this tumor to induce an elevated serum phosphatase is now well understood and the activity of the tumor is roughly

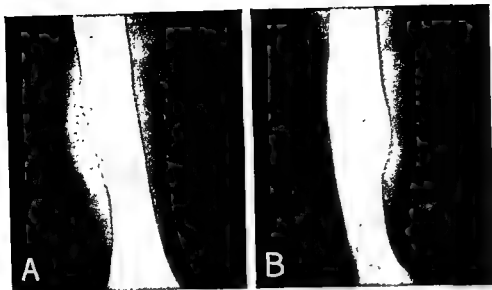


FIG. 151. Chondrosarcoma of the humerus. Note great difference in the anteroposterior and lateral views.

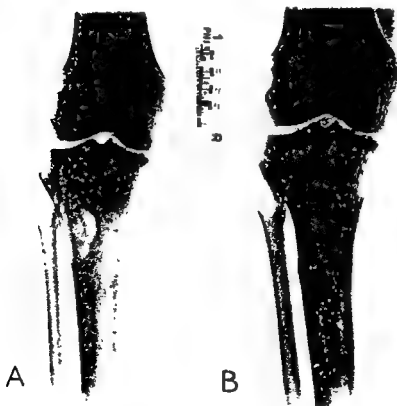


FIG. 152. Low-grade chondrosarcoma developing on central chondroma. A shows the appearance of the lesion preoperatively. The operation consisted of curettage, application of zinc chloride, and sliding bone transplant. The result four years later is shown in B. The patient is well more than six years, and has a limb with unimpaired function.

proportional to the phosphatase level. This level often diminishes markedly after heavy radiation and falls to normal limits after amputation, provided there are no metastases.



FIG. 153. Chondrosarcoma of lower femur. Primary chondroblastic type in a young adult male. (Letterman General Hospital)

The microscopic appearance is variable, but there is cartilage and pre-cartilaginous connective tissue present in which there are areas of myxomatous or cystic degeneration (see Figs. 153 and 154). The more anaplastic and undifferentiated the tissue, the more malignant the tumor. Indeed, some completely undifferentiated osteolytic sarcomas placed in the osteogenic group may well belong with the primary chondrosarcomas. This is rather an academic point and has little clinical importance.

SECONDARY CHONDROSARCOMA

This variety of malignant sarcoma of cartilaginous origin is nearly always seen in adults; it results from a malignant alteration in the cells of a cartilaginous exostosis, a central chondroma, or rarely, in a patient who has multiple skeletal defects such as hereditary deforming dyschondroplasia.

of the malignant area is usually easy. This is one of the commoner varieties of primary malignant sarcoma of the skeletal system (see Figs. 156-168) encountered in patients over 35 years of age.



FIG. 156. Enormous chondrosarcoma of femur, slowly-growing, and neglected (Courtesy of Dr. Arthur Krida, Bellevue Hospital, New York.)



FIG. 157. . Central chondromyxosarcoma of upper femoral shaft. This lesion probably developed on a benign chondroma.

Many of Morton's cases fall into this group; he found the mean age of the 74 cases he reported was 38 years. The male sex is more often affected. In addition to the marked variation in growth rate and degree of malignancy

nancy of these secondary chondrosarcomas their histologic appearance is also quite variable (see Fig. 170). There may be much fibrous and myxomatous material interspersed with cartilage; irregular calcification may be



FIG. 158. Gross specimen of central chondrosarcoma of sternum. Patient, a male of sixty, had a tumor of the sternal region that remained stationary for thirty years before becoming malignant. The growth had penetrated the posterior sternal cortex to form a soft-part mass lying in the anterior mediastinum. The tumor was resected with most of the gladiolus and ensiform.

prominent and readily demonstrated in the roentgenogram. Different portions of the same tumor may show entirely different pictures. The more

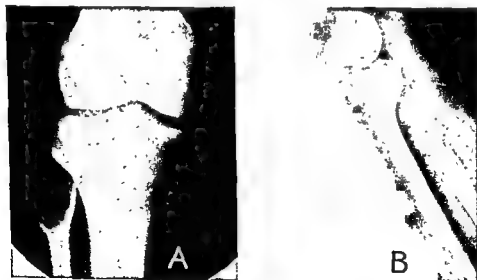


FIG. 159. Appearance of lesion regarded as giant cell tumor and treated by roentgen therapy with relief of symptoms. Later the character of the tumor changed and after a biopsy the limb was amputated. Final diagnosis, *chondromyxosarcoma*.

cellular and anaplastic areas are usually found at the periphery. The central portion may be necrotic, calcified, or ossified. In typically hyaline areas

the lacunar cells are ovoid, in myxomatous areas the cells are spindle shaped or stellate. All sorts of pleomorphism may appear; binucleate forms, nucleate, and even true tumor giant cells have been described by Morton.



FIG. 160. Secondary chondromyxosarcoma on basis of preexisting chondroma of acromial end of clavicle. These tumors are relatively slow-growing at first and may be cured by early amputation or resection. In this case, permission for early operation was withheld and when later done elsewhere the result was metastasis and death.

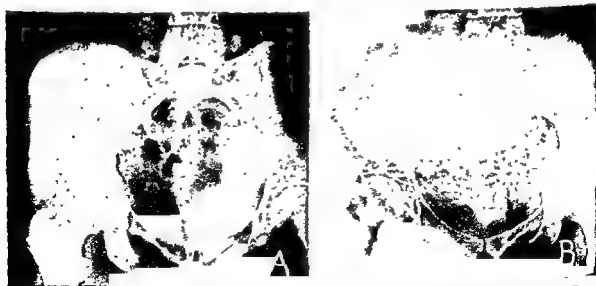


FIG. 161. A, Early osteochondroma of ilium. Appearance in 1936. (Letterman General Hospital.) B, Same case, 1943, showing condition seven years later: inoperable, causing severe pressure symptoms. This case illustrates the relentless, progressive growth of these low-grade cartilage tumors and emphasizes the necessity of surgical attack in the early stages of the disease.

Mitoses in considerable numbers are rarely seen. Much variation exists in the vascularity of these tumors.



FIG. 162. A, Chondrosarcoma of scapula in an albino Negro. B, Lateral view of same patient. C, Roentgenogram of the same case taken for bone detail. D, Appearance of the patient following total scapulectomy. The wound could not be completely closed and pinch grafts had to be used. E shows preservation of useful function of upper extremity following total scapulectomy.

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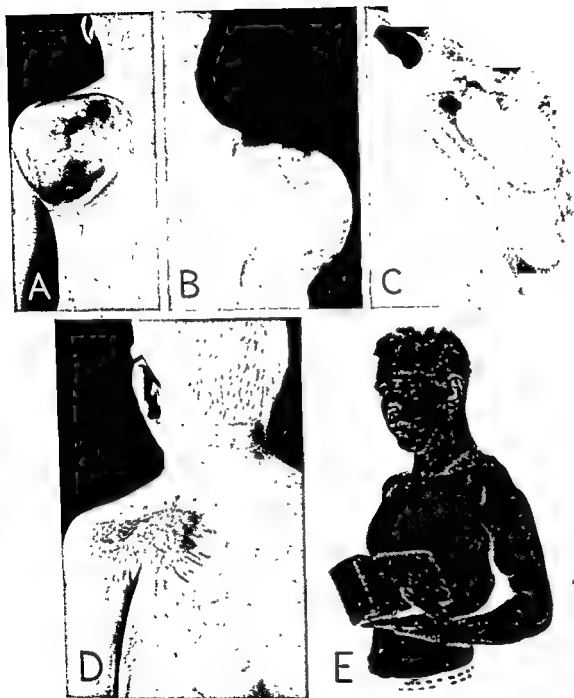


FIG. 162. *A*, Chondrosarcoma of scapula in an albino Negro. *B*, Lateral view of same patient. *C*, Roentgenogram of the same case taken for bone detail. *D*, Appearance of the patient following total scapulectomy. The wound could not be completely closed and pinch grafts had to be used. *E* shows preservation of useful function of upper extremity following total scapulectomy.

The report of benign chondroma from a biopsy may be misleading; it is dependent upon the character of tissue removed and a study of the entire tumor might disclose that other areas are frankly malignant. The systematic

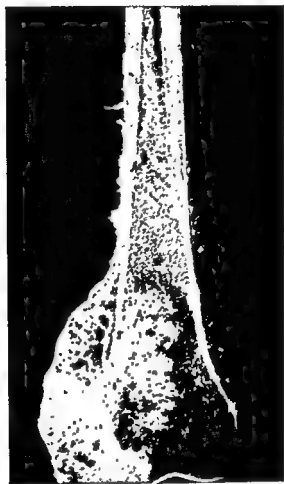


FIG. 163. Chondrosarcoma in a 19-year-old male. Amputation through upper fourth of femur has been followed by a fifteen-year survival.

removal of benign chondromas or osteochondromas may be a life saving measure, comparable to the successful treatment of other precancerous lesions (see Fig. 33, p. 96).

Central chondromas of the phalanges, on the other hand, almost never become malignant. Morton had one such case but we have never encountered an example. Conservatism in the handling of phalangeal cases is therefore justified.

Chondrosarcoma of tendon origin is extraordinarily rare; cases have been reported by Jones, Kienbock, Buxton, and Geschickter and Copeland. It has been suggested that they are derived from undifferentiated precartilaginous areas. The histologic features of chondrosarcomas developing in these extraosseous locations do not differ from those seen in the ordinary skeletal forms of the disease.



FIG. 164. A, Chondromyxosarcoma of head of humerus arising as a central tumor. Appearance prior to surgical biopsy. B, Same case three years later. Treatment in the interim by high-voltage X-ray. Now on the border line of operability. C, Appearance of shoulder at the time roentgenogram shown in B was made. *Note* fungation and ulceration of tumor through the skin which had been heavily irradiated. Even at this stage a successful interscapulothoracic disarticulation was performed but the patient ultimately died of pulmonary metastasis.

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TREATMENT

We are in agreement with Morton's categorical statement that "surgery is the only effective means of treatment of chondrosarcoma." However, we



FIG. 165. Chondrosarcoma: a peculiar form developing after several local resections of a parosteal tumor which was histologically entirely benign at first (osteochondroma). Successive removals yielded increasingly less benign-appearing tissue until finally an amputation was performed. Following this, lung metastasis developed.

do not consider amputation as definitely indicated in every case of chondrosarcoma of a bone of the extremity. Much depends upon the physical setting of the individual case. For chondroblastic sarcoma, amputation is generally the only safe procedure. For secondary chondromyxosarcomas in such bones as the fibula or ulna, wide resection can be done without much greater loss of function than that following simple excision of the tumor-bearing area. In a case of thrice-recurrent central chondroma of borderline malignancy that had been treated unsuccessfully by curettage, a wide segmental resection with substitution of a massive tibial graft has been followed by a ten-year survival with an excellent functional result (see Fig. 36, p. 101). For successful conservative surgery, however, great care must be exercised in the selection of cases and the utmost attention paid to complete removal of the tumor-bearing bone.

Attempts have been made to conserve the limb by performing resection of the diseased portion of a long bone. Phemister has removed a segment of the shaft of the femur, and, by using two large bone transplants, one

taken from each tibia, he has obtained an excellent functional as well as anatomic result and a long survival. The upper end of the humerus has been removed for osteogenic sarcoma with the upper fibula transplanted to make

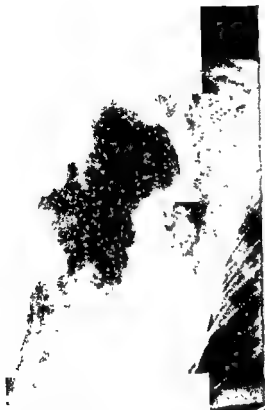


FIG 166. Low-grade chondrosarcoma in a 71-year-old male, who had sustained a fall on the arm one year previously. Skull films show areas suggesting Paget's disease. Section reveals a very low-grade chondrosarcoma. Pathologist said he would need to examine the films to go beyond "cellular chondroma."



FIG. 167. Spindle cell sarcoma with some cartilaginous element. The biopsy taken three and a half years prior to amputation did not reveal the lesion in recognizable form and clinically and roentgenographically it was regarded as a chronic nonsuppurative osteomyelitis.

good the defects. Chondrosarcomas of the scapula have been subjected to total scapulectomy with an occasional brilliant result; in one case so treated, the patient has survived more than eleven years with a useful upper extremity (see Fig. 169).

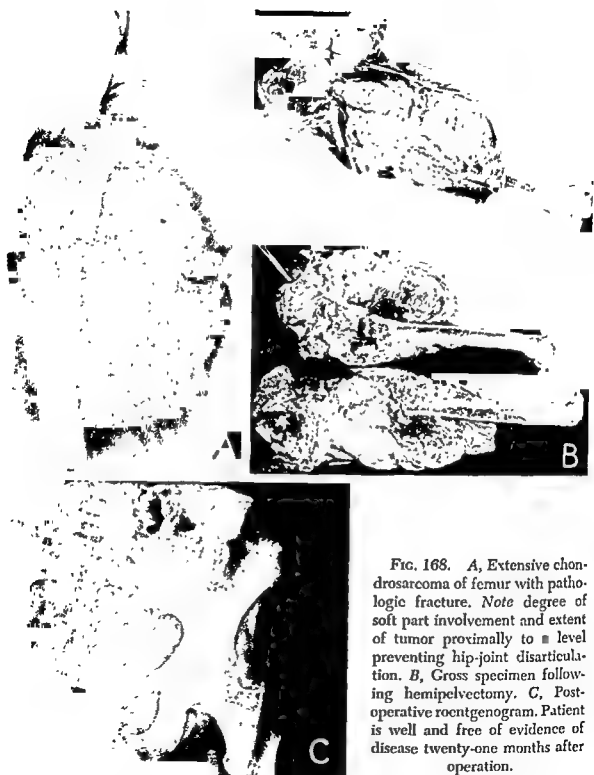


FIG. 168. *A*, Extensive chondrosarcoma of femur with pathologic fracture. Note degree of soft part involvement and extent of tumor proximally to a level preventing hip-joint disarticulation. *B*, Gross specimen following hemipelvectomy. *C*, Post-operative roentgenogram. Patient is well and free of evidence of disease twenty-one months after operation.

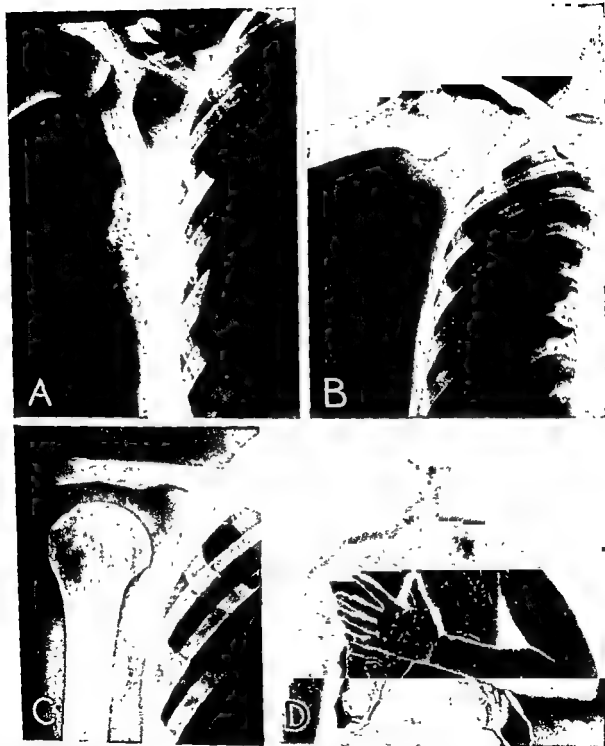


FIG. 169. Chondromyxosarcoma of scapula. *B*, Appearance following partial scapulectomy. Note irregularity of the margin of the scapula fragment adjacent to the line of division; this represented a local recurrence. *C*, Result following total scapulectomy. *D*, Result one year later. Patient still well with a useful upper extremity eleven years after last operation.

It should be emphasized that these conservative operations will not be successful if attempted without most careful selection of cases. Low-grade fibrosarcomas and central chondromyxosarcomas represent the only clear-

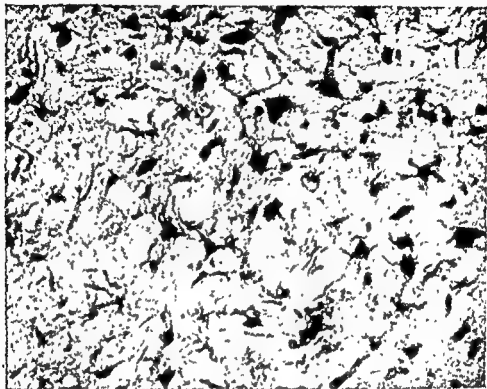


FIG. 170. Microphotograph of chondromyxosarcoma. A low-grade type made up largely of stellate or polygonal cartilage cells embedded in mucoid matrix.

cut indications for attempting resection as an alternative to amputation. In upper extremity bones especially, such a conservative course is more justified and it is believed that in the future such attempts as have been mentioned will be made more often.

Exceptional cases may be encountered where a transformation of a benign osteochondroma into a malignant chondrosarcoma has taken place and where it may be possible to resect or excise the tumor through a base of uninvolved bone. One such opportunity was afforded in a tumor of the lower femur, and the patient was spared an amputation; there has been no recurrence or metastasis for more than nine years (see Fig. 155, p. 285).

It is only fair to point out the fact that the cases in which it is possible to substitute a conservative operation for an amputation are relatively infrequent; and it requires experience and the cooperation of an able pathologist to select these cases from the majority in which the more radical measure of amputation is definitely indicated.

23. ENDOTHELIOMA OF BONE (EWING'S SARCOMA)

CLASSIFICATION AND ETIOLOGY

THIS IS A PRIMARY MALIGNANT NEOPLASM OF BONE WHICH WAS FIRST recognized by Lücke in 1866. Some three decades later Hildebrandt and Markwald published separate reports on unquestioned cases, while in America, Howard and Crile (1905) gave an account of 23 cases, 4 of which had been personally observed. In 1916, Symmers and Vance described in detail a case which they thought bore some resemblance to multiple myeloma.

This tumor was at first designated as *round cell sarcoma* but during the past twenty-five years it has become established as a distinct clinical entity. Ewing in 1921 called our attention to the clinical, roentgenographic, pathologic, and therapeutic aspects of the tumor and did more than any other investigator to enhance our knowledge of the condition which now bears his name.

Certain clearly distinctive characteristics make it possible to separate endothelioma from other primary tumors of bone: its predilection for children and adolescents, for males rather than for females, for the shaft rather than the ends of long bones, its roentgenographic appearance, its tendency to metastasize to other bones as well as to the lungs, its marked radiosensitivity, its characteristic histologic pattern, and its exceedingly unfavorable prognosis. The etiology of this tumor, as of other sarcomas, remains obscure. However, observers have repeatedly noticed cases in which its earliest symptoms and signs suggested an underlying infectious process (fever, leukocytosis) and we have wondered whether some obscure infection such as a virus may not be a factor in the development of endothelioma.

At all events, the differential diagnosis between an osteomyelitis and endothelioma of bone remains among the most difficult in the entire field of bone tumors.

This difficulty is true not only from the clinical and roentgenographic standpoints but, at times, from the histologic as well. Cases have been ob-

served in which early sections revealed inflammatory tissue without any suggestion of tumor while later in the course of the disease there was unquestioned microscopic confirmation of the presence of endothelioma.



FIG. 171. Endothelioma of clavicle. Hemisection of gross specimen.

A series of registered cases studied by Connor showed 40 per cent with a distinct history of early signs pointing to inflammation as the etiologic factor. He showed that the histologic appearance of tissue seen in these cases may be indistinguishable from inflammation of bone.

Ewing's sarcoma does not produce either cartilage or bone. Where new bone is found in relation to this tumor it is reactive bone rather than tumor bone; it is indistinguishable from healing or inflammatory bone and is due to a reparative effort of the bone-forming elements. Degenerating bone surrounded by tumor cells represents destruction of the normal architecture of the cortical lamellae (see Fig. 171). These processes occurring simultaneously give rise to the characteristic roentgenographic appearance; they also account for the erroneous impression that this tumor does produce bone.

Endothelioma is so radiosensitive that even a single exposure to roentgen-rays prior to biopsy has been responsible for errors in diagnosis; the microscopic picture has been so altered that the pathologist has been unable to make a correct diagnosis. The appearance is then one of necrosis that could be interpreted as osteitis or inflammation. No recognizable tumor cells are seen. Experience, therefore, shows it to be imperative that

no radiation should be employed until biopsy has revealed the presence of endothelioma; we do not share the preference of some writers for "test radiation" in lieu of biopsy (see Figs. 172 and 173).



FIG. 172. Endothelioma of fibula. This case was regarded as osteomyelitis and operated upon elsewhere by drill holes and packing.

Finally, it must be reemphasized that the distinction between this condition and subacute infection of bone can be a most difficult one to make. The two should be borne in mind when dealing with a young patient complaining of pain, swelling, destruction of bone, slight fever, and leucocytosis.

AGE, SEX, DISTRIBUTION

This tumor occurs more frequently than is generally realized. Next to osteogenic sarcoma it is the most common primary malignant tumor of bone. We have records of 149 cases at Memorial Hospital (see Fig. 174). It occurs twice as frequently in the male as in the female. It is an affection of childhood and adolescence, with the great majority of cases occurring under the age of 25, and the period of from 10 to 15 years has the highest

incidence. In the past, cases have been reported occurring in older people, even up to the age of 86. It is the writer's strong conviction that these cases were not examples of endothelioma but of some other condition of which

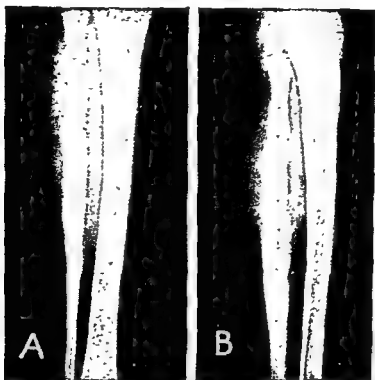


FIG. 173. Endothelioma of fibula in a girl of 7. A shows the condition at a time when clinical, roentgenographic and even histologic evidence favored an inflammatory lesion. B shows the change that took place in a period of three years. Total duration from onset to death was three years and two months. Final diagnosis confirmed by the Registry was Ewing's sarcoma. (See case report, p. 317.)

reticulum cell sarcoma is the most probable. Certainly, in a patient over 30 years of age, one should be extremely hesitant about accepting a diagnosis of endothelioma of bone. Differentiation from reticulum cell sarcoma of bone is difficult; while most pathologists are in agreement with Ewing that they are different tumors, Oberling and also Stout regard them as variants of the same tumor. This difference of opinion is no doubt responsible for the latter including among the Ewing's sarcomas cases occurring in late middle life. It is our opinion that reticulum cell sarcoma and endothelioma are not only different diseases but that they ordinarily occur at a different age. Also their prognosis is different; the reticulum cell sarcoma is not uncommon in middle or later life and the outlook is not nearly so gloomy as it is in the case of Ewing's sarcoma.

Morton's findings in 190 cases collected from the Bone Sarcoma Registry indicate that the bones of the lower extremity are affected more frequently than are the rest of the skeleton combined and twice as often as those of the upper extremity (Table XXVII).

CLINICAL FEATURES

The triad of symptoms common to other malignant bone tumors is found here: pain, swelling or "lump," and disability. The degree of pain is more

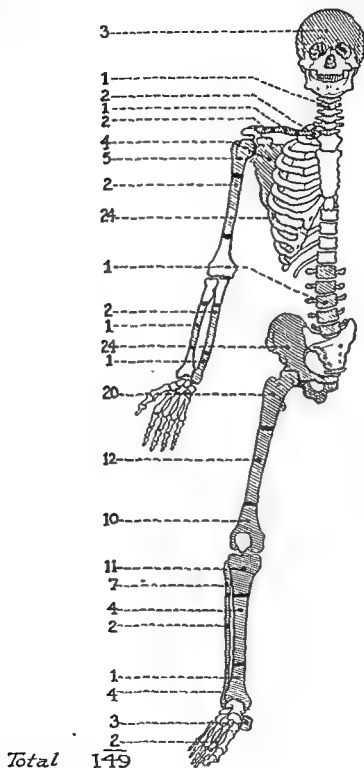


FIG. 174. Distribution of primary tumor in 149 cases of endothelioma.

variable and the interval between pain and the first discovery of the tumor is often shorter than is the case in osteogenic sarcoma. Disability is incon-

stant and less prominent as an early symptom. Fever of irregular and intermittent type, often accompanied by leucocytosis, may be present.

TABLE XXVII

DISTRIBUTION OF ONE HUNDRED AND NINETY EWING'S SARCOMAS*

<i>Lower Extremities</i>	<i>Cases</i>
Tibia	39
Femur	38
Fibula	16
Foot—small bones	7
Patella	1
	<hr/>
	101
<i>Upper Extremities</i>	
Humerus	19
Clavicle	8
Scapula	7
Radius	5
Ulna	4
	<hr/>
	43
<i>Axial Skeleton</i>	
Pelvis	25
Ribs	13
Spine	6
Skull	1
Jaw	1
	<hr/>
	46

* MORTON, J. J. The treatment of Ewing's sarcoma of bone. In PACK, G. T., and LIVINGSTON, E. M. Treatment of Cancer and Allied Diseases. New York, Paul B. Hoeber, Inc., 1940, p. 2422.

Reference has already been made to the fact that endothelioma may be readily confused with bone infection. Its onset is often insidious. Many cases are operated upon by means of incision and drainage, and, when frank pus is not obtained, the surgeon removes some tissue from which the pathologist is able to arrive at the correct diagnosis. Its progress varies markedly, being exceedingly rapid in some cases, while in others a fatal termination may be long deferred. The average life expectancy is less than two years. Morton has called attention to its inclination to grow in spurts followed by periods of relative quiescence. The tendency of this tumor to yield to adequate X-ray therapy, although temporarily and as far as the primarily treated area is concerned, is widely recognized. Ewing was one of the first to call attention to the responsiveness of endothelioma to both radium-pack and roentgen-ray treatment. In this respect the tumor, which is composed of uniformly small round cells, reacts as do cells of the lymphoid series. At least one can regard it as responding as do primitive, undifferentiated cells of high malignancy.

A most discouraging feature of this tumor is its proclivity for metastasizing to other bones—often the skull (see Fig. 175)—to the lungs, and sometimes to the lymph nodes and viscera as well.

The location of the primary lesion is often a diagnostic lead. While it is

common to find it arising in the metaphyseal region of a long bone of the lower extremity, it extends toward the diaphysis which may be quite extensively involved.



FIG. 175. Metastatic endothelioma of cranial bones.



FIG. 176. Endothelioma of fibula. Note position of lesion in midshaft and presence of reactive new bone.

ROENTGENOGRAPHIC APPEARANCE

While much has been written concerning the peculiar roentgenographic features of endothelioma and its easy differentiation from other tumors, especially from osteogenic sarcoma, it is the writer's opinion that it may be exceedingly difficult to decide between these two conditions, and that some of the criteria previously given as characteristic must be considered as too inconstant to be of great value. Extent of bone involvement and situation in shaft have been cited as points in favor of endothelioma (see Figs. 176 and 177). Reactive bone is generally laid down in layers (plywood or onion-skin appearance) parallel to the shaft, which is not the case with

osteogenic sarcoma, where radiating spicules project at right angles from the cortex like the sun's rays. Expansion of the shaft of the bone may occur in both conditions, but it is more commonly seen in endothelioma. The

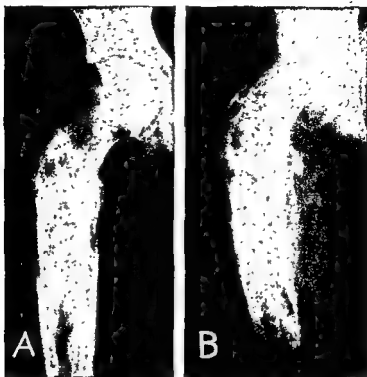


FIG. 177. Endothelioma of femur. The appearance in A was strongly suggestive of infection rather than tumor. Following a mild exposure to roentgen therapy a biopsy revealed no evidence of tumor. This was construed as favoring the diagnosis of bone infection and it was not until twelve months later that the appearance seen in B aroused grave suspicion, prompting another biopsy which established the diagnosis of endothelioma.

lesion at first may resemble bone infection or osteogenic sarcoma (see Figs. 178-183).

While the diagnosis in a classical case can often be made from films alone, a considerable proportion of cases present less typical roentgenographic features; these may resemble osteomyelitis, osteogenic sarcoma (osteolytic type), chondroblastic sarcoma, reticulum cell sarcoma, metastatic neuroblastoma, luetic periostitis, and other inflammatory bone conditions. Hence the clinical features and laboratory findings must receive close scrutiny in conjunction with the roentgenograms. When a flat bone, such as the ilium or scapula, is affected the appearance is difficult to interpret.

HISTOLOGIC EXAMINATION

Early biopsy and microscopic examination are necessary to confirm clinical and roentgenographic impressions and should be resorted to promptly and unhesitatingly, although the precautions concerning the closure of open biopsy wounds are particularly applicable here (see Fig. 184).

The aspiration method is nearly always successful in these cases, and should often be considered in preference to an open surgical biopsy (see Chap. 3, p. 31).



FIG. 178. Endothelioma of femur, showing wide extent of bone involvement, location in midshaft, and marked similarity to periostitis (for which it was first mistaken on roentgenographic examination). This exemplifies the difficulty encountered in trying to distinguish between Ewing's sarcoma and inflammatory lesion of bone.

FIG. 179. Endothelioma of femur. Note the manner in which the cortex is lamellated, giving the appearance sometimes described as "onion skin." The involvement extends over almost one-half of the shaft of the bone.

The untreated endothelioma should be capable of accurate microscopic diagnosis in most instances. Reticulum cell sarcoma has been frequently mistaken for endothelioma, and in one instance a case of Hand-Schüller-Christian's disease was classified as a Ewing's sarcoma until the long survival caused the pathologist to revise his diagnosis to reticulum cell sar-

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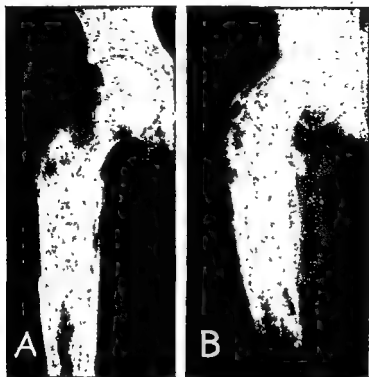


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FIG. 182. Endothelioma of scapula.



FIG. 183. Endothelioma of pubis (autopsy confirmation). (Beaumont General Hospital.)

coma and ultimately to call it eosinophilic granuloma. It is therefore quite possible that other supposed cures of endothelioma may represent similar cases of histologic misinterpretation. Metastatic neuroblastoma in a long



FIG. 180

FIG. 180. Endothelioma of radius.



FIG. 181

FIG. 181. Endothelioma of tibia in a patient aged thirty. Note that the characteristic roentgenographic features are lacking. The lesion was thought to be inflammatory until biopsy established it as an Ewing's sarcoma.

bone may give rise to difficulties in microscopic interpretation. That such mistakes readily occur in highly trained hands must be recognized. In truth,



FIG. 182. Endothelioma of scapula.



FIG. 183. Endothelioma of pubis (autopsy confirmation). (Beaumont General Hospital.)

the more expert and highly qualified the pathologist, the more willingly he acknowledges the factor of human error in the histologic diagnosis of this tumor.

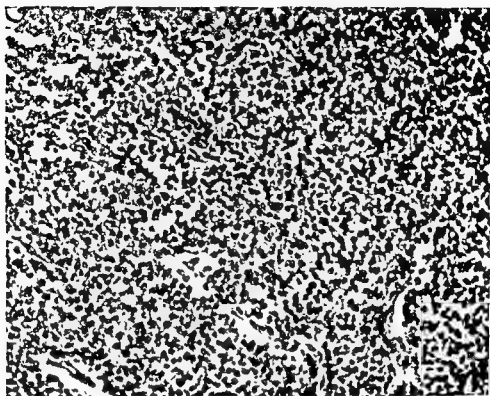


FIG. 184. Microphotograph of endothelioma. Diffuse growth of rather small round cells. Some suggestion of vasoformative properties.

TREATMENT

The treatment of this condition must be admittedly predicated on the extremely small prospect of permanent eradication. The fact that profound alterations in tumor cells can be produced by doses of roentgen rays that are not destructive to normal tissue must also be taken into consideration. Accompanying this effect on the tumor cell there is regression of the swelling and relief of pain and disability, all of which may occur with remarkable swiftness. Adequate roentgen-ray treatment of the primary lesion is nearly always followed by dramatic and lasting regression. It must be acknowledged, however, that unless therapy has been carefully administered in full doses local reactivation may occur and, when it does, further therapy is less effective and may fail to control the growth.

Unfortunately, despite the control of the primary tumor, metastases nearly always develop later, and though these in turn yield to treatment the patient is unable to tolerate the continuing hopeless struggle to keep up with the widespread disease by radiation therapy. No case of unques-

tioned diagnosis has, to the writer's knowledge, been cured by radiation alone. Surgical extirpation, which includes resection or amputation, must therefore be considered a primary method of treatment; it may be preceded by moderate doses of radiation.

RADIATION THERAPY

Since the almost universal acceptance of roentgen rays as being more economical than radium pack, and fully as effective for treating extremity tumors, the trend has been toward high-voltage X-rays. Radium pack has consequently been seldom used of late and its technic will not be discussed here.

Roentgen Therapy

Several practical points have been learned by past experience. Regardless of the extent of the disease as seen in the film, one must assume that the actual involvement is much greater. Therefore it is wise to outline for treatment the entire length of the affected bone (see Fig. 185). Fractional dose technic, using two or more portals, is the present method of choice. While amounts, both as to daily dose and total dose, vary considerably in the hands of different radiologists, it is desirable to give maximal total dosage at one course rather than to give less and repeat later on. It is certainly clear that this tumor can develop radioresistance when less than maximum dosage is employed. For further details see the



FIG. 185. Endothelioma of humerus. Note the pigmentation of the skin following heavy radiation. The lesion first appeared in the upper portion of the humerus and the portals used for therapy were not large enough to cover the entire diseased part. After marked regression the disease recurred in the mid-portion of the shaft and was much more radioresistant. Tumors of this type should always receive radiation throughout the entire length of the shaft of the bone.

chapter on irradiation, page 553.

SURGICAL TREATMENT

If one accepts the fact that endothelioma is localized at first to one area in a bone and that subsequent foci are metastases and not separate tumors originating *de novo*, then immediate amputation should be the method of choice. Actually the results of amputation in this disease are notoriously poor.

We have reluctantly concluded that immediate amputation as a routine measure is scarcely justified but if it is done then it should (in contrast to osteogenic sarcoma) be invariably performed at a level proximal to the



FIG. 186. Endothelioma of fibula prior to treatment. See Fig. 285 C, p 493.

bone which is involved, even if it means that a hip joint disarticulation is required. This is essential because in this disease the tumor extends widely and affects bone far beyond the point where clinical and roentgenographic involvement is evident.

Resection

While few authorities have stressed the possibility that conservative surgery has a place in the treatment of Ewing's sarcoma, we have long felt

that wherever possible resection of the primary tumor should be given a trial. If thereafter the patient fails to develop recurrence within the field of operation, the conservative operation must be regarded as successful in

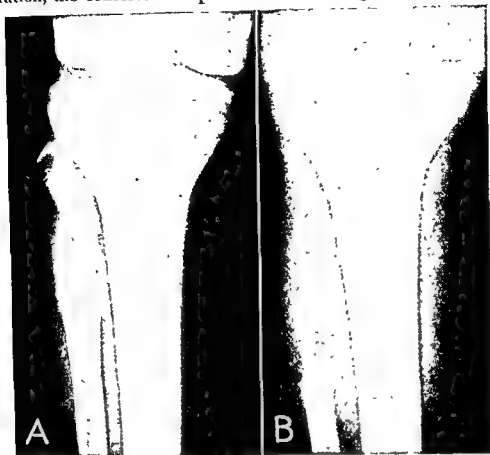


FIG. 187. A, Endothelioma of fibula. B, Same case seven months after treatment, which consisted of mild preoperative roentgen therapy following open biopsy, then resection followed by several courses of Coley's toxins. Patient is well with a useful limb nine years after treatment.

removing the primary growth and considered justified as a substitute for amputation even though the ultimate outcome is death from metastases. A number of personal cases have been treated by such means and have not shown regional recurrence (see Figs. 186-188).

It is urged that this practice be given a more extended trial in tumors primary in the fibula, ulna, scapula, and perhaps occasionally in other bones such as radius and humerus. Certainly the mutilating operation of amputation seems one to be avoided assiduously wherever possible since it offers the patient with Ewing's sarcoma such a gloomy prospect of survival.

If resection is to be selected as the form of surgery, it has seemed advisable to precede it by a single course of a moderate amount of roentgen therapy. This has not proved a hazard in attaining prompt wound healing. Heavy dosage, especially if repeated, is definitely contraindicated and in such circumstances failure of the wound to heal might of itself affect the outcome by making a later amputation necessary.

After regression has taken place following moderate radiation, resection can be performed, and when wound healing is complete, considerable further radiation may be given without fear of wound breakdown.



FIG. 188. A, Endothelioma of scapula. B, Same case after total excision of scapula

Primary wound healing should be the aim in every operation for a bone tumor. This cannot be emphasized too strongly.

TOXIN TREATMENT

The value of Coley's toxins is still much debated and apparently not yet firmly established. For one reason, the accepted five-year survivals have without exception received other forms of therapy, i.e., surgery or radiation, alone or combined, in addition to toxins. Yet the fact that toxins were used in 3 of our 4 cases and in 8 of the 11 in the Bone Sarcoma Registry (1940) that survived for five years makes it difficult to accept the statement made by Geschickter and Copeland that "Coley's toxins have no effect on the duration of life, either when given alone or combined with other forms of treatment."

It is considered that the toxins may exert some influence upon minute metastases which will prevent the latter from establishing themselves in the bed in which they have lodged; it is less likely that this inhibitory effect occurs in large primary tumors or in extensive well-established metastases. The extreme vascularity of this neoplasm is probably an important reason for the effective action of the toxins. Radiation renders the tumor much less vascular and for this reason it would seem logical that if the toxins are to be used they should precede radiation therapy. If the primary lesion is

operable, toxin treatment should be used after resection or amputation for the possible inhibitory effect this agent might have upon minute and unrecognized metastases.

When metastases are present, it is justifiable to administer Coley's toxins for a period of several weeks. If no improvement is evident at the end of that time they should be discontinued and roentgen therapy given to all foci, using portals designed to prevent unnecessary exposure of uninvolved tissue, particularly in the lungs (see Chap. 58, p. 565).

PROGNOSIS

Survival after the disease is first recognized averages about two years. There are but few examples of five-year recoveries in which the diagnosis was established beyond a doubt. In 1940, for example, the author studied the Bone Sarcoma Registry cases that had remained well for five years or more and found only 11 cases that Stewart considered to be unequivocal. These are summarized in Table XXVIII. Tables XXIX and XXX present the experience at Memorial Hospital.

TABLE XXVIII

ENDOTHELIOMA FIVE-YEAR SURVIVALS IN BONE SARCOMA REGISTRY AS OF MAY, 1940

TOTAL: 11 cases; sex, 6 males, 5 females	
AGE: Youngest, 7 years; oldest, 46 years; average, 17 years (if the case aged 46 is omitted, the average is 14.1)	
BONE INVOLVED:	
Tibia	Cases 3
Fibula	2
Femur	2
Humerus	1
Scapula	1
Jaw	1
Rib	1
INTERVAL FROM ONSET OF SYMPTOMS TO ADMISSION AND TREATMENT:	
Shortest	3 days
Longest	18 months
Average	4 months
METHODS OF TREATMENT EMPLOYED:	
Surgical.	
Amputation	7
Excision or resection	4 (3 preceded amputation—fibula, femur, humerus 3 without amputation—jaw, scapula, rib)
Radiation:	
Without surgery	1 (also had toxins)
Preoperative	1
Postoperative	4
Pre- & postoperative	1
Not stated which	1
Toxins:	
Preoperative	1
Postoperative	2
Both	2
Without surgery	1 (also had X-ray)

TABLE XXIX
FIVE-YEAR SURVIVALS OF ENDOTHELIOMA OF BONE (EWING'S SARCOMA)*

NAME	AGE	SEX	BONE	PATHOLOGIC DIAGNOSIS	SURGERY	ROENTGEN THERAPY	TOXINS	SURVIVAL PERIOD	DEAD OR ALIVE
T. B. L.	8	M	Left tibia	Endothelioma	Mid-thigh amputation	Yes	Yes	5 yrs. 6 mos.	Dead of sarcoma
	13	M	Right humerus	Endothelioma	Biopsy only	Yes	Yes	9 yrs. 10 mos.	Alive
A. P.	19	M	Right tibia	Endothelioma	Low-thigh amputation	Yes	Yes, also P ₂₈	5 yrs. 5 mos.	Alive
H. V.	48	M	Right tibia	Endothelioma	Osteotomy; diagnostic curettage	Yes	Yes	8 yrs. 10 mos.	Alive
B. C.	22	M	Left fibula	Endothelioma	Excision end of tibia	Yes	No	6 yrs. 6 mos.	Alive
W. B.	14	M	Right fibula	Osteogenic or endothelioma	Excision of proximal portion fibula	Yes	Yes	7 yrs. 6 mos.	Alive

* Memorial Hospital series 1919-1941 inclusive Compiled May, 1947.

TABLE XXX
ENDOTHELIOMA OF BONE*

	1919-1933	1930-1941	TOTAL
Clinical diagnosis	115	21	136
Without histologic verification	37	1	38
With histologic verification	78	20	98
a. Indeterminate Group			
1. Dead of other causes in less than 5 years without recurrence	0	0	0
2. Lost to follow-up without recurrence	0	0	0
b. Determinate Group			
1. Failures:			
(a) Dead of sarcoma	72	16	88
(b) Lost to follow-up with disease	2	2	4
(c) Dead of other causes but with disease	0	0	0
(d) Postoperative deaths	0	0	0
2. Successes.			
(a) Free of disease 5 or more years after treatment	4 ^b	2	6
Five-year survival rate (determinate group)	5.1%	10%	6.1%

* Memorial Hospital series, 1919-1941 inclusive. Table compiled as of May, 1947.

^b One patient died of sarcoma 5½ years later.

CASE REPORTS

Case 1. Endothelioma of Humerus

L. L., male, age 13 years, came under our care at Memorial Hospital and the Hospital for Special Surgery¹ in 1936 with the following history: In March, 1935, first complained of pain in the right shoulder which gradually increased in severity and was not relieved by physiotherapy. In early July, 1935, an aspiration biopsy was done at Crown Heights Hospital, Brooklyn, from which a diagnosis of sarcoma was made; this was confirmed at the Jewish Hospital, Brooklyn. During August, 1935, roentgen therapy (total of 3740 r) was administered to the right shoulder.

Physical examination on admission to Memorial Hospital (May 15, 1936) revealed an old, well-healed, wide scar located on the anterior aspect of the upper right arm. Directly under the scar was a firm nodular tumor mass apparently connected with the bone. The entire upper right arm was larger than the left. Motion was fairly free and there was no pain on palpation or percussion in the upper arm or shoulder. A provisional diagnosis of Ewing's tumor was made (see Fig. 189A).

From a study of submitted films, Dr. Herendeen was inclined to regard it as osteogenic sarcoma. He stated that the disease extended from the epiphyseal line down the shaft for a distance of approximately four inches and involved principally the cortex externally. A submitted section was examined by Dr. Fred Stewart who reported it to be an endothelioma of bone. (On further study five years later he reaffirmed this diagnosis.)

Treatment:

Roentgen therapy from Apr. 20-30, 1936, 1500 r to each of 3 ports, right upper humerus

Coley's toxins from May 5 to June 10, 1936, a total of 20 injections in doses ranging as high as $\frac{1}{10}$ minim intravenous and 8 minims intramuscular

Roentgen therapy July 9-18, 1936, 2500 r to each of 3 ports, right upper humerus

¹ Then called the Hospital for Ruptured and Crippled.

Coley's toxins from Jan. 17 to Feb. 2, 1937, 14 injections increased to a dose of 8 minims intramuscular

A radiographic report on July 1, 1936, states: "Definite improvement. The



FIG. 189. Endothelioma. Diagnosis conformed by open biopsy. A, Appearance prior to treatment. B, Condition ten years after treatment by high-voltage X-ray therapy and Coley's toxins. Aside from slight underdevelopment of the upper arm the result is excellent and the patient is symptom free.

medial and especially the lateral margin of the involved area shows bone regeneration, and a more definite demarcated border. There is no evidence of the periosteal elevation previously present. Chest films are negative for metastasis."

The patient continued in excellent health to May, 1946, or ten years after the beginning of treatment. At this time films of the chest were negative for pulmonary metastasis and those of the humerus revealed a completely quiescent, apparently healed area at the site of the sarcoma (see Fig. 189B).

This is Case 2238 in the Bone Sarcoma Registry.

Case 2. Endothelioma (Ewing's Sarcoma) of Fibula

H.S., male, age 8 years, was admitted to Memorial Hospital on Oct. 26, 1920, with the following history: In January, 1920, while at play the patient was struck in the right ankle by a sled. Pain was soon felt in this region and a roentgenogram revealed bone involvement which was interpreted as osteomyelitis. A biopsy specimen, however, obtained in the latter part of May was diagnosed as osteosarcoma. The tumor continued to increase in size with great rapidity, and despite the fact that the inguinal nodes were found to be involved, an amputation at the middle third of the femur was performed on June 5, 1920. Later one of the inguinal nodes was excised and found to be of the same type sarcoma as the

amputated specimen. Treatment with Coley's toxins was begun in early July and continued for about one month. Two months later a large tumor was demonstrable in the iliac fossa, and a film of the chest showed what was considered to be pulmonary metastasis. Radiation in the form of radium pack, totalling 10,000 millicurie hours, was applied at 6 cm. over the iliac fossa but no treatment was given over the chest. The prognosis was regarded as entirely hopeless. However, within a few weeks the mass in the groin disappeared and the patient regained his normal weight and strength. Examination on Dec. 21, 1921, failed to reveal any evidence of tumor over the abdomen, groin, or chest. He continued in good health for the next fourteen years and then succumbed to an acute attack of appendicitis with peritonitis in January, 1935, fifteen years after the onset of his original illness.

The diagnosis of endothelioma of bone made by Dr. Ewing was confirmed by the Bone Sarcoma Registry (Case 267).

Case 3. Endothelioma (Ewing's Sarcoma) of Fibula

F.K., female, age 7 years, was first seen at Memorial Hospital on May 15, 1931, complaining of slight pain in the right leg. The first symptom, swelling, had been discovered by her mother two weeks previously. A physician was consulted who had a roentgenogram made; this disclosed a diffuse lesion in the shaft of the fibula which was thought to be an endothelioma (see Fig. 173A, p. 300).

Physical examination on admission to Memorial Hospital revealed a fusiform indurated mass measuring about 4 x 8 cm. situated on the outer aspect of the right leg over the fibular area. A roentgenogram showed a diffuse lesion involving substantially all the cortex of the fibula with bone formation and cortical reaction characteristic of Ewing's sarcoma in its earliest stages. Comparative measurements of the circumference of both legs 10 cm. below the patella revealed an increase of 2.25 cm. on the affected side.

There was considerable difference of opinion on the part of those who saw the patient as to whether the condition was one of chronic inflammation of bone or Ewing's sarcoma. Divergent views were expressed by Doctors James Ewing, Francis Carter Wood, William B. Coley, and Ralph Herendeen. Unfortunately it was finally decided to treat the patient with roentgen therapy and a tumor dose estimated at 1380 r was given through separate portals of 762 each on two occasions (May 25 and 28, 1931). Marked improvement followed. No pathologic material was obtained until a surgical biopsy was performed on July 29, 1931. This was reported as "chronic osteitis—no tumor." The wound healed per primam and in view of histologic diagnosis no further treatment was given.

Occasional examinations in the Outpatient Department during the next two years failed to disclose any activity on the part of the lesion, and the patient presented no symptoms. A roentgen-ray treatment of 300 r was given in July, 1933. Ten months later the symptoms in the right leg returned and a second biopsy (this time by aspiration) was performed. This revealed an endothelioma. Despite further roentgen therapy and a course (15 injections) of Coley's toxins, the disease continued to progress; it metastasized to the mandible and caused death on July 22, 1934.

The foregoing case is an excellent illustration of the injudicious use of radiation prior to the establishment of the diagnosis by histologic examination. The original roentgen therapy had so altered the tissue that both the pathologist and the Bone Sarcoma Registry regarded it as inflammatory rather than neoplastic. Figure 173 (p. 300) shows the roentgenographic appearance of the fibula in 1931 and 1934.

An equally puzzling case involving the femur, in which the histologic diagnosis was made unreliable by preliminary radiation, is illustrated in Figure 177 (p. 304).

24. ANGIOSARCOMA OF BONE

MORE THAN TWENTY YEARS AGO THE TERM "ANGIOENDOTHELIOMA" WAS applied by Kolodny to certain primary tumors of bone; at the same time he emphasized the confusion that existed between this term and "angiosarcoma." The former has been linked with that of diffuse endothelioma, as a subdivision of Ewing's sarcoma. It is now our belief that sufficient evidence exists to justify the recognition of angiosarcoma of bone as a rare primary skeletal neoplasm, but that the term "angioendothelioma" should be abandoned since it is by no means certain that the few cases in which this diagnosis has been made were not actual examples of metastatic carcinoma, metastatic neuroblastoma, or even liposarcoma.

The distinction between angiosarcoma and angioendothelioma was first suggested and employed by Thomas, and we feel that accumulated statistics apparently warrant it. A recent review of the files of Memorial Hospital reveals 11 cases which we believe rightly belong in this category. Of these 7 have been classified as angiosarcoma and 4 as angioendothelioma. Three of the 7 angiosarcomas appear to have arisen on the basis of a benign angioma. There were 6 males and 5 females in the combined groups; the ages varied from 8 to 50 years. The scapula was involved in 3 cases, the femur, humerus, and rib in 2 each, and the metatarsal and tibia-fibula each in 1 case. As is usual in most malignant tumors of bone, pain was the first symptom; this was followed promptly by swelling, a prominent feature, so that by the time the patient sought medical advice, a definite tumor was apparent. Pulsation was not observed although bruit was noted in one instance. The regional lymph nodes were not affected.

The roentgenologic features of angiosarcoma and angioendothelioma are not readily distinguishable from other types of malignant bone disease; for example, they may resemble telangiectatic osteogenic sarcoma, reticulum cell sarcoma, or metastatic carcinoma, and may be difficult if not impossible to differentiate from the classical Ewing's sarcoma. Eosinophilic granuloma is a benign lesion that may offer difficulty in the differential diagnosis. In fact we know of no instance in which angiosarcoma has been correctly diagnosed save by histologic study.

The treatment employed in this small group of cases was variable so that it is difficult to draw any definite conclusions as to therapy. We believe, however, that early removal of the tumor-bearing portion of the bone is

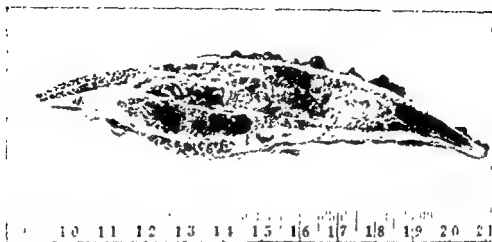


FIG. 190. Gross specimen of angiosarcoma of rib, showing marked expansion and distortion of normal outline of bone. The vascular tumor tissue is represented by the dark areas in the central portion of the tumor.

indicated since these tumors are less radiosensitive than Ewing's sarcoma of bone. This wide removal may be accomplished in the case of a scapula by total scapulectomy, and in the case of a rib by resection of the involved rib together with the two adjacent ribs; but as a general rule, amputation is required.

In the 11 cases described, 3 survived for more than five years.

The clinical features of both angiosarcoma and angioendothelioma are sufficiently similar to permit of their consideration together; indeed, the major differentiation lies in the pathologic interpretation. While it seems possible for pathologists to state categorically that a tumor is an angiosarcoma of bone, in our 4 cases of angioendothelioma the latter diagnosis was rendered as a preference or a probability, with that of metastatic hypernephroma or metastatic carcinoma suggested as a possibility. There is no great clinical importance in separating these two unusual neoplasms from the more frequently observed Ewing's sarcoma but if, as a result of biopsy, the pathologist can make a definite diagnosis of angiosarcoma then surgical measures may be instituted promptly in preference to irradiation; whereas if Ewing's sarcoma is reported, the reverse may be true.

Ewing, who was largely responsible for the revised classification of bone sarcoma, did not provide a special designation of angiosarcoma but included angioendothelioma as one of the subdivisions of endothelioma, the tumor which now bears his name. Foote and Anderson have called attention to the vasoformative properties retained by a case of endothelioma of the rib which they consider supports Ewing's thesis that this tumor origi-

nates from vascular endothelium. DeSanto recorded a case which he thought lent support to the view that Ewing's tumor had its origin in lymphatic endothelium of the Haversian canals and was therefore a lymphangioendothelioma. According to Hauser, in a group of 12,000 autopsies performed at Cleveland City Hospital only one case of angiosarcoma of bone was found. He believes that the final diagnosis of angiosarcoma of bone depends upon the microscopic observation of a malignant endothelial tumor with distinct vasoformation. Geschickter and Copeland have not included this entity at all in their *Tumors of Bone*.

25. MULTIPLE MYELOMA (PLASMA CELL MYELOMA)

MORE THAN A HUNDRED YEARS AGO HENRY BENCE-JONES RECEIVED FROM Sir James Watson a sample of urine that had been obtained from a 45-year-old male patient. He recognized that it contained a strange substance which was then called "animal matter" but which has since become known as Bence-Jones protein. This case was reported by MacIntyre in 1850.

Rustizky (1873) was apparently the first to describe this condition as multiple myeloma and Kahler (1889) is said to have been the first to point out the association of Bence-Jones proteinuria and myeloma.

This malignant tumor of bone marrow arises from cells normally present in the marrow itself. It is characterized by multiple foci and is found chiefly in males between the ages of 40 and 60. No cases are recorded in children.

CLASSIFICATION

Lubarsch's original enumeration of four varieties is still in use and is given in the classification of the Bone Sarcoma Registry. It is repeated here for convenience:

1. Plasma cell myeloma
2. Myelocytoma
3. Lymphocytoma
4. Erythroblastoma

Of these, the first, or plasma cell variety, is by far the most frequent, constituting more than 95 per cent of all myelomas. In fact, the others are extremely rare tumors and case reports are meager. For practical purposes the clinician need give but little concern to them and should consider plasma cell myeloma as the probable form whenever a myeloma is suspected. Microscopic studies are required to differentiate one from the other.

AGE AND SEX

The average age of the patients with this disease is about 60 years, although it is encountered in those between 40 and 80 years; it is rarely seen

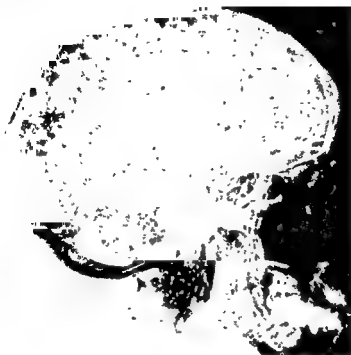


FIG. 191. Plasma cell myeloma of skull.

in subjects as young as 35 years. Males are much more often affected, in the proportion of three to one.

ETIOLOGY

There is no definite information available concerning the cause of this group of tumors. Some observers consider that it is a disease of the blood-forming apparatus rather than a true tumor. Certain cases present characteristics which suggest a leukemic process. The plasma cell variety has been regarded as malignant lymphoma. Lubarsch, one of the earliest pathologists to investigate this disease, concluded that myeloma is not a true blastoma but a systemic disease of the lymphatic-hemopoietic system and closely related to leukemia. The possibility of its being fundamentally a nutritional disorder which may have an endocrine basis must remain conjectural.

CLINICAL FEATURES

Pain is unquestionably the most constant, the earliest, and often the only symptom complained of. It is variable at first but tends to become progres-

sive and is distinctly aggravated by activity and relieved by rest; in contrast with other malignant bone neoplasms it is uncommon at night.

The locations most frequently complained of are the chest and the lower back; the latter is readily accounted for by the fact that the ribs, sternum, and lumbar spine (the chief site of red marrow) are so uniformly affected. Tenderness is often a striking finding and is not necessarily indicative of pathologic fracture.



FIG. 192. Collapse of cervical vertebra due to plasma cell myeloma.

Pathologic fracture is common in this disease, especially if one takes into account the buckling or telescoping of vertebral bodies and the slight inflections of the ribs. We have observed bilateral femoral fracture as well as fracture of both clavicles. Bayrd and Heck found a surprisingly low incidence of fracture in their series of 83 cases, i.e., 16 per cent. Sudden, unexplained pain in the spine in a patient

over 40 years of age should arouse suspicion of a partial collapse of a vertebra; pain in the chest, of a pathologic fracture of a rib due to myeloma. In such cases, lacking complete skeletal roentgenographic examination, an occasional spine fusion has been done under the assumption that tuberculosis of the spine was present.

The secondary anemia, which in diffuse myelomatous involvement is constant and often quite marked, is readily explained on the basis of encroachment of tumor cells on the available hemopoietic centers in the red marrow. Weakness, lassitude, and anorexia are common symptoms; fever is occasionally noted and albumosuria is variable.

ROENTGENOGRAPHIC APPEARANCE

The characteristic feature of this disease is the presence of multiple discrete areas of radiolucency which give the appearance of being punched out of the bone. There is no condensation at the periphery. These lesions are sharply demarcated. The areas are of central origin, produce no periosteal reactive bone as a rule, and are resorptive in nature (see Figs. 191-196). When solitary lesions exist they may reach a greater size and be less characteristic so that they may resemble other bone conditions. Other lesions giving rise to multiple punched-out areas of bone destruction have to be considered. Of these, metastatic carcinoma of osteolytic type is by far the most common. Here a roentgenographic differential diagnosis may be impossible but the history and the chemical studies of the blood may be

of great assistance. Microscopic study of a section or of material obtained by aspiration will generally yield a positive diagnosis. Hyperparathyroidism is mentioned as simulating myeloma roentgenographically but this has not



FIG. 193. Plasma cell myeloma of humerus and glenoid.



FIG. 194. Solitary plasma cell myeloma of humerus. At the time this film was taken skeletal X-rays were negative for any other bone involvement. However, the patient later developed other bone lesions and succumbed.

been our experience. Blood-chemistry determinations will readily establish the diagnosis. Endothelioma has also been mentioned in the differential diagnosis but it seldom occurs past the age of 30 while myeloma is seldom seen below the age of 40. Moreover, the roentgenographic appearance is dissimilar; myeloma involves little or no bone response whereas endothelioma splits the cortex and causes extensive reactive bone formation.

LABORATORY FINDINGS

The presence of Bence-Jones proteinuria is strongly suggestive of this disease although it occurs rarely in other conditions, such as leukemia, metastatic cancer of the bone, fibrocystic disease, postmenopausal osteoporosis, multiple bone sarcoma, and comminuted fracture. On the other hand, a negative test has little meaning since it occurs in about half of the cases.

Secondary anemia is common. A patient with unexplained anemia should be investigated as a possible case of plasma cell myeloma.

Chemical determinations of the blood are of course indicated in any



FIG. 195

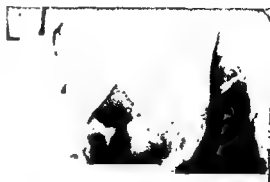


FIG. 196

FIG. 195. Plasma cell myeloma of ilium. No other lesions have developed during an observation period of almost seven years.

FIG. 196. Plasma cell myeloma of mandible.

suspected case of bone disease. An elevation of the serum protein is often found although alterations in the serum alkaline phosphatase, serum inorganic phosphorus, and serum calcium are too inconstant to be of any diagnostic value. The sedimentation rate is, however, consistently increased so that a normal reading is strong presumptive evidence that the disease is not present. The albumen globulin ratio may be reversed.

HISTOLOGIC STUDY

Until recently the final proof of the existence of plasma cell myeloma depended on the report of the pathologist based on biopsy material obtained from an area of bone involvement (see Fig. 197). Sternal marrow puncture is a simple method of obtaining cells, has a broad application, and should be employed in preference to formal surgical biopsy which may be unnecessary provided positive findings are secured. Negative results from a single sternal marrow puncture do not rule out the existence of the disease. Rubinstein and Silver have recommended iliac marrow puncture as a highly satisfactory substitute for sternal marrow puncture (see p. 40).

TREATMENT

No form of treatment has as yet been discovered which can be considered a cure. Among the methods which have been tried are roentgen

therapy, Coley's toxins, radioactive phosphorus, and, most recently, the diamidine compounds (stilbamidine and pentamidine) combined with a diet low in animal protein.

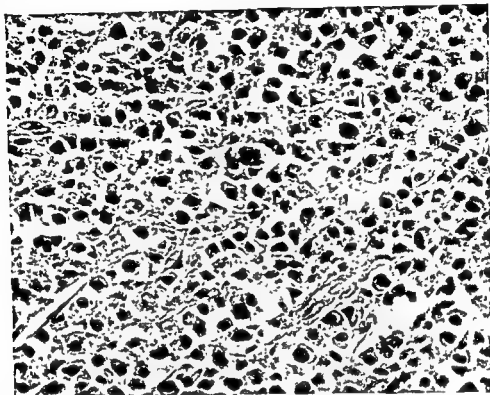


FIG. 197. Microphotograph of plasma cell myeloma. Tumor made up of both typical and atypical plasma cells.

Despite the uniformly fatal prognosis in this disease and the fact that surgical measures are illogical, it can be said that relief of pain and perhaps some prolongation of life can be accomplished by using moderate doses of high-voltage roentgen therapy. Only those areas which are extensive and are causing symptoms should receive treatment. It should not be given—contemplating a cure—in doses sufficient to kill the ordinary cancer cell. These patients often have a marked decrease in the available hemopoietic cells in bone marrow due to replacement by cells of the myeloma. To irradiate large areas indiscriminately serves to increase the difficulty under which the red-cell-forming mechanism is laboring.

Cases with a solitary area in the ilium have been given moderate roentgen therapy through several portals, and cycles have been repeated at intervals of from four to six weeks. Some of these patients have had a rather remarkable clinical course with comparative comfort over a period of one to three or more years. This has not been so striking where the disease has become widespread.

Every effort should be made to avoid pathologic fracture, especially of a major long bone or vertebral body, for such a complication greatly in-

creases the patient's discomfort and adds to the difficulties of nursing care. Spinal support by a removable plaster corset or a brace of the Taylor type is indicated when destruction of bone is detected before actual collapse occurs. For lesions in the femur a walking caliper splint is of value in protecting against fracture (see Fig. 107, p. 193).

Transfusions are of only temporary benefit in combatting the more severe degrees of anemia.

Bayrd and Heck maintain that no treatment exerts a palliative effect on this disease. Improvement of the local areas of bone destruction by roentgen therapy has been frequently observed at Memorial Hospital; pain has been relieved and pathologic fractures have reunited. Whether or not in cases so treated the ultimate fatal outcome is postponed by the use of roentgen therapy is doubtful since there is a limit to the area of red marrow which can be irradiated without harmful effects upon its hemopoietic activity.

Snapper reports worthwhile relief of pain from stilbamidine and pentamidine given in connection with a diet low in protein to 15 patients with multiple myeloma. All were suffering excruciating pain prior to the treatment; 13 were confined to bed. In all there was considerable relief of pain, and 11 were able to walk at the time of their discharge from the hospital. The remarkable clinical improvement persisted in 1 case for eighteen months; in another there was a relapse sixteen months after the first treatment. In other patients relapses were successfully treated by further courses of stilbamidine. No satisfactory explanation has been offered for the manner in which these diamidine compounds act. It is known that during and after treatment myeloma cells can be demonstrated. Persistence of Bence-Jones protein in the urine and of the increased globulin content of the urine is reported by Snapper who asserts that "the treatment even at best only checks the disease temporarily and does not cure it."

PROGNOSIS

We know of no case of multiple myeloma which may be said to have been permanently cured. There is an average expectation of about eighteen months from the time the patient first presents symptoms. However, there are examples of strikingly long survival. One of our cases lived eleven years after the diagnosis was made by an open biopsy for what was then considered a solitary lesion. Other cases have been personally observed which have lived five years. It cannot be explained upon the basis of the treatment they received and the only fact that seems to be evident is that these cases were apparently examples of so-called solitary plasma cell myeloma when first discovered, and that generalization did not occur until after the lapse of considerable periods of time.

26. SOLITARY PLASMA CELL MYELOMA

ONE MAY FIND OCCASIONAL REFERENCES IN THE LITERATURE TO CASES OF solitary plasma cell myeloma. Assurance of the accuracy of this diagnosis seems quite impossible. What is undoubtedly meant is that careful roentgenographic examination of the entire skeleton discloses only a single bony lesion caused by this disease. These cases actually are not uncommon in our experience and it is the rule that if followed carefully they will exhibit other areas of bone destruction later in the course of the disease. We have been struck with the apparent predilection of these "solitary" lesions for the ilium but have also observed instances where the middle third of the humerus and the neck and trochanteric area of the femur were affected. These cases may easily be mistaken for metastatic carcinoma and occasionally for fibrocystic disease of bone. One should recognize, however, that bone changes capable of detection on the X-ray film may be only manifestations of the disease—which is fundamentally one of the soft tissues of the red marrow—and consequently may not be truly significant of the extent of the condition. We are now treating a patient in the advanced stage of the disease whose bone marrow is obviously severely damaged and who has a marked secondary anemia and impaired kidney function of a pronounced degree; yet skeletal films reveal only a single indistinct bone lesion in the body of a lumbar vertebra. Hence, while some cases of "solitary" plasma cell myeloma seem to run a course that is more prolonged and milder, this is not invariably true and in any event the final outcome is unaltered.

In a review of the literature in 1939, Pasternack and Waugh found 30 cases of solitary myeloma to which they added 1 of their own. They divided these cases into two groups: (1) those which began as a solitary lesion but later produced generalization of the disease, and (2) those which remained cured or arrested without evidence of other areas of involvement for a prolonged period of time. This latter group they felt deserved the term *solitary myeloma*.

The bone involved in these cases was as follows:

	<i>Cases</i>
Femur	8
Ilium	7
Humerus	5
Vertebra	4
Maxilla	2
Parietal bone	2
Tibia	1
Clavicle	1
	<hr/> 31

Bence-Jones proteinuria was present in 13 per cent. In two other instances it appeared later after the disease had become widespread.

The roentgenographic appearance in two-thirds of this series was strongly suggestive of giant cell tumor, while in the majority of the remainder bone cyst was simulated.

PROGNOSIS

The principal significance of these solitary myelomas lies in the improved prognosis. Seven of the 31 cases were known to be alive for periods ranging from four to ten years (6 were alive from seven to ten years).

It is impossible to correlate the various modes of treatment which these cases received with the favorable results. Various combinations of surgery and radiation therapy were employed.

When the diagnosis of solitary myeloma has been established histologically we feel that one should incline toward a more favorable prognosis, at least in point of life expectancy, than is justified in the average case of multiple myeloma.

27. RETICULUM CELL SARCOMA OF BONE

PARKER AND JACKSON, IN THEIR COMMUNICATION IN 1939, FIRST DESCRIBED reticulum cell sarcoma of bone as a specific disease entity. It is a relatively rare tumor as shown by the fact that the original report included only 17 cases collected from three large Boston hospitals and the records of Memorial Hospital contain only 23 cases. A search of the literature since 1939 discloses only four papers on this subject.

Reticulum cell sarcoma arises in both long and flat bones but the majority involve the shaft of a long bone, particularly the metaphyseal portion, although, like Ewing's sarcoma, it extends into the diaphyseal area. It is osteolytic, destroying the cortex; where new bone is produced, it is reactive rather than tumor bone. Its growth is rapid. Metastasis takes place both to the lungs and, less frequently, to lymph nodes.

Personal experience covering a series of 23 cases shows that there were 14 males and 9 females. The age incidence is shown in Table XXXI. It is much more frequent in youth and early adult life. The predilection for long bones is also shown in the same table

CLINICAL FEATURES

Pain is the first symptom which is true of nearly all forms of bone sarcoma. A nontender swelling in a patient with a normal blood picture, without accompanying fever, and in a young person in good health should prompt the taking of roentgenograms of the affected area and of the lungs. When an irregularly destructive, frequently expansile tumor is found in which the cortex is fragmented and overlying muscles are invaded the suspicion that the condition is reticulum cell sarcoma should lead to microscopic confirmation and, if there is doubt in the interpretation of the histology, recourse should be had to several opinions from pathologists experienced in tumors of bone (see Fig. 198). This neoplasm is composed of sheets of cells with round, oval, or indented nuclei which are nearly twice as large as those in endothelioma of bone.

TABLE XXXI

PRIMARY RETICULUM CELL SARCOMA OF BONE*

No.	Name	Year of Admission	Sex	Age	Bone	Treatment	Metastases	Result	Follow-up
1	G. B.	1925	M	31	Tibia	Amputation, Toxins	Amputation Stump, Regional Lymph Nodes, Skin of Abdomen	Alive, N.E.D. ^a	20 years
2	R. E.	1934	M	17	Tibia	H.V.X-ray, Toxins	None	Alive, N.E.D.	13 yrs
3	W. B.	1937	M	14	Scapula	H.V.X-ray, Toxins	None	Alive, N.E.D.	10 mos
4	W. M.	1937	M	47	Sternum	H.V.X-ray, Toxins	None	Alive, N.E.D.	10 yrs
5	D. R.	1938	M	16	Femur	H.V.X-ray, Toxins	None	Alive, N.E.D.	2 mos
6	E. D.	1941	F	18	Femur	H.V.X-ray	None	Alive, N.E.D.	10 yrs
7	J. C.	1943	F	13	Fibula	Resection Fibula	None	Alive, N.E.D.	1 mo
8	A. F.	1943	M	63	Rib	H.V.X-ray Postop H.V.X-ray	None	Alive, N.E.D.	5 yrs
9	L. L.	1944	M	23	Lumbar Vertebra	H.V.X-ray	None	Alive, N.E.D.	1 mo
10	S. C.	1945	F	8	Femur	H.V.X-ray, Toxins	None	Alive, N.E.D.	3 yrs
11	S. M.	1941	F	21	Tibia	H.V.X-ray	None	Alive, N.E.D.	3 yrs
12	J. S.	1946	M	54	Tibia	H.V.X-ray, Amputation (No Regional Tumor in Specimen)	None	Alive, N.E.D. (Last Report 1943)	5 mos
13	S. R.	1946	F	21	Humerus	H.V.X-ray, Toxins	None	Alive, N.E.D.	3 yrs
14	T. L.	1947	M	37	Tibia	H.V.X-ray	None	Alive, N.E.D.	1 mo
15	E. B.	1947	F	24	Femur	H.V.X-ray	None	Alive, N.E.D.	2 yrs
16	D. S.	1947	F	25	Ilium	H.V.X-ray, Toxins	None	Alive, N.E.D. (Last Report 1943)	5 mos
17	C. V.	1947	M	28	Tibia	H.V.X-ray	None	Alive	1 yr 8 mos
18	J. A.	1942	F	18	Humerus	H.V.X-ray, Toxins	Regional Lymph Nodes, Upper Thigh, Abdominal Wall (On Admission)	Alive, Marked Improvement	11 mos
19	P. B.	1930	M	53	Humerus	H.V.X-ray, Toxins (Palliative)	None	Under Treatment	9 mos
20	W. H.	1937	M	55	Scapula	H.V.X-ray, Radium Element Pack	Regional Lymph Nodes, Including Iliac (On Admission)	Under Treatment	6 mos
21	M. O.	1940	F	59	Ilium	H.V.X-ray, Radium Pack (Palliative)	Lungs, Skin of Upper Arm	Died with Disease	3 mos
22	S. T.	1932	M	11	Scapula	Radium Element Pack (Palliative)	Skull, Liver, Ribs, Brain (?)	Died, Pul. Hemorrh. Pt. had T.B.	2 yrs
23	V. R.	1929	M	14	Femur	Radium Element Pack (Palliative)	Skin of Chest Wall	Died with Disease	7 mos
							Buttocks, Pelvis, Thigh (On Admission)	Died with Disease	1 yr
							Kidneys, Jejunum, Stomach, Mesentery (Autopsy)	Died with Disease	9 mos
							Skull, Lungs (On Admission)	Died with Disease	11 mos
								Died with Disease	7 mos
								Died with Disease	5 mos
								Died with Disease	21 mos

* Memorial Hospital series, 1915-1947

^a N.E.D. signifies No evidence of disease

It is of importance to call attention to the fact that reticulum cell lymphosarcoma, which is a disease having its inception in lymph nodes, not infrequently metastasizes to bone and when it does, the clinician must decide

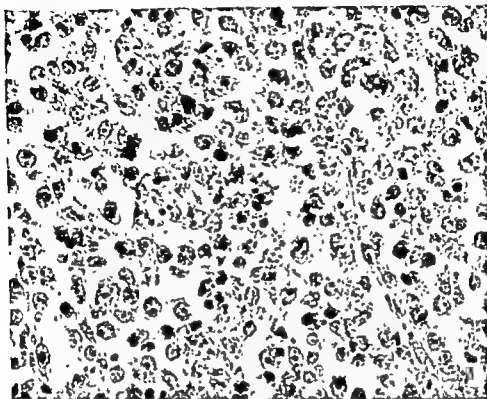


FIG. 198. Microphotograph of reticulum cell sarcoma of bone. Indifferent growth pattern. Large reticulum cells form the predominating cellular element.

whether he is dealing with this situation or whether the case is one of primary reticulum cell sarcoma of bone with metastases to lymph nodes. This is often a difficult decision and in some of the cases at Memorial Hospital it is a matter of conjecture. From the group of cases in our files at Memorial Hospital in which there was demonstrable bone involvement and microscopic diagnosis of reticulum cell sarcoma we have excluded those which, from the evidence at hand, seemed to have commenced in lymph nodes with secondary involvement of bone. Table XXXI gives the details of 23 cases which we consider to be primary in bone. Many of these have never shown any evidence of lymph node involvement.

ROENTGENOGRAPHIC FEATURES

The literature prior to 1947 contains no comprehensive study of the roentgenographic diagnosis of reticulum cell sarcoma of bone. Those authors who do refer to it indicate that the roentgenographic findings are of little or no diagnostic aid. With this view we are not in accord. While admitting the difficulties associated with a correct roentgenographic diagnosis we have found it possible at Memorial Hospital to interpret the films in this disease



FIG. 199. Reticulum cell sarcoma of lateral condyle of femur. Note the irregular osteolytic pattern which has been likened to a "cracked-ice" appearance



FIG. 200. Reticulum cell sarcoma of upper third of shaft of humerus. Note shadow of soft-part tumor and changes in texture of bone



Fig. 199. Reticulum cell sarcoma of lateral condyle of femur. Note the irregular osteolytic pattern which has been likened to a "cracked-ice" appearance.



Fig. 200. Reticulum cell sarcoma of upper third of shaft of humerus. Note shadow of soft-part tumor and changes in texture of bone.

with a fair degree of accuracy. A study of 17 cases from the standpoint of roentgenographic appearance has led Sherman and Snyder to the belief that by this means the diagnosis may perhaps be reached or at least suggested.

This tumor is medullary in its origin but destroys cortex as well as medulla and has little tendency to provoke periosteal reactive new bone formation. The destruction is responsible for a finely granular or patchy osteolytic process (see Figs. 199-203) and the shaft of the involved bone is usually somewhat widened producing a fusiform enlargement.

There have been instances in our experience where the films in proven cases of reticulum cell sarcoma of bone closely resembled those of metastatic carcinoma although, as pointed out by Sherman and Snyder, the tumor to which it bears the closest resemblance is medullary osteolytic osteogenic sarcoma. At times it closely mimics an inflammatory process, such as eosinophilic granuloma, and occasionally, when some lamellation of the affected cortex has occurred, it may be mistaken for Ewing's sarcoma.

DIFFERENTIAL DIAGNOSIS

Many of these tumors in the past were classified as "round cell sarcoma" and later as "endothelioma." This is still a difficult distinction to make because the roentgenographic appearance is similar and the microscopic picture is also easily confused. There are some pathologists who maintain that these two lesions are identical and they hold that Ewing's sarcoma is actually a reticulum cell sarcoma (see Fig. 204).

In a recent review of the Bone Sarcoma Registry material, Stewart considered 3 of the 15 five-year survivals of Ewing's sarcoma to be reticulum cell sarcoma. Thus it is evident that the average clinician or pathologist will continue, for some time at least, to find it difficult to decide between these two primary bone sarcomas. Nor is the



FIG. 201. Reticulum cell sarcoma of tibia. Note wide extent of shaft involvement. Following roentgen therapy an amputation was performed and the pathologist found no residual viable tumor cells.

roentgenologist in any better position to make this decision for the roentgenographic appearance of Ewing's sarcoma differs so much in individual cases that it is difficult to point out features that clearly indicate whether



FIG. 202. Reticulum cell sarcoma of bone. This case presented as a large fusiform swelling of the knee and seemed clinically to be of synovial origin, i.e. synovioma. Surgical biopsy revealed reticulum cell sarcoma. (Ashburn General Hospital.)

the case in question is reticulum cell sarcoma or Ewing's sarcoma.

If the patient is over 35 years of age there is strong likelihood that the tumor is reticulum cell sarcoma and not Ewing's sarcoma. Cases are seen that present roentgenographic features of osteomyelitis while others simulate osteogenic sarcoma. For the most part, however, the roentgenologist has been unable to classify these cases further than to suggest that they are malignant tumors. It will be noted that in 50 per cent of the cases the tibia or femur was the site of involvement.

TREATMENT

Since this is a radiosensitive tumor it is felt that the primary growth should be given full therapeutic doses of roentgen therapy rather than being treated by amputation.

Resection followed by radiation has been employed successfully in cases of Ewing's sarcoma occurring in favorable locations and it is probable that in reticulum cell sarcoma such conservative measures may occasionally be justified.

Parker and Jackson recommended immediate amputation followed by radiation of regional lymph nodes. In our experience, however, there have been comparatively few instances of lymph-node involvement.

Further experience with different forms and combinations of surgery and radiation is needed before definite conclusions can be drawn regarding the method of choice. Coley's toxins have been used in conjunction with sur-



FIG. 203. Primary reticulum cell sarcoma of humerus in a 21-year-old female.

gery or radiation. In 1 of our cases in which the method employed biopsy, radiation, and toxin therapy the lesion in the tibia has remained well and the patient is without evidence of disease eleven years later is our present belief that roentgen therapy supplemented by injection of Coley's toxins is the most acceptable method of treatment for reticulum cell sarcoma.

PROGNOSIS

Reports indicate a definitely more favorable outlook for recovery from this disease than is true of Ewing's sarcoma. For this reason, particularly it is important to make a differential diagnosis between the two conditions.

Second course of toxins begun August 5, 1926—large doses, kept up, with rest intervals of a few weeks, until by November, 1926, his condition had so improved that he had gained 30 pounds in weight, the metastatic areas had disappeared and the stump circumference had decreased by 35.5 cm. On December 5, 1926, he was discharged.

Subsequently, as a precautionary measure, he received two more courses of toxins in 1927.

Patient has remained well and has never exhibited any further evidence of recurrence or metastasis. He was heard from in 1945, or 19 years after the toxins were first begun, 20 years after the unsuccessful amputation.

The reader can obtain further details by referring to the following articles dealing with this most unusual case:

Christian, S.L., and Palmer, L.A.: *Mil. Surgeon* 90:42, 1927.

Coley, W.B.: *Ann. Surg.* 85:615, 1927.

Christian, S.L., and Palmer, L.A.: *Am. J. Surg.* 4:188, 1928.

Meyer, W.: *Cancer*. New York, Paul B. Hoeber, Inc., 1931, pp. 347-349.

Coley, W.B.: *Glasgow M.J.* 128, Sept., 1936.

Bone Sarcoma Registry, Case 1143.

Case 2

R. E., a 17-year-old male, first complained of pain in the right knee in June, 1934. Swelling was noted three months later and on Sept. 4, 1934, a biopsy was taken and repeated two weeks later. Sections were later reviewed at Memorial Hospital and a diagnosis of reticulum cell sarcoma of bone was made. The tibia presented roentgenographic evidence of a destructive bone lesion. X-ray therapy was administered at Hahnemann Hospital, Philadelphia, as follows:

Date	No.	Time	Kv.	Ma.	Distance	Time	Filter	Conditions
10/ 3/34	1	15	175	4	55 cm.	15	0.5 Cu 1.0 Al	Ant. to upper half r. tibia
10/ 5/34	2	10	"	"	"	20	"	Int. and ext. to r. tibia
10/ 9/34	1	15	"	"	"	15	"	Ant. to upper half r. tibia
10/12/34	1	15	"	"	"	15	"	Post. to upper half r. tibia
10/17/34	2	10	"	"	"	20	"	Int. and ext. to half r. tibia
10/22/34	2	15	"	"	"	30	"	Ant. and post. to upper half r. tibia

On admission to Memorial Hospital in October, 1934, the patient was found to be an extremely tall youth, walking on crutches and complaining of constant pain at the tumor site for which sedation was required.

The knee could not be flexed beyond 85 degrees or extended beyond 170 degrees. He presented two vertical biopsy wounds on the anterior aspect of the upper tibia. The lateral incision was completely healed, the medial one was healed in part but the lower two-thirds was the site of an area of unhealthy granulation tissue with slough present at one point. Very little soft part swelling was present but the tibia in the affected portion was diffusely widened.

He was given twenty-six doses of Coley's toxins from Oct. 31, to Nov. 30, 1934, with chills and temperature elevations following the injections. Seven of the injections were given by intramuscular and nineteen by intravenous route.



FIG. 205. Reticulum cell sarcoma of upper tibia twelve years after treatment with roentgen therapy and toxins following open biopsy. Excellent functional result.

He has remained well for twelve years and in 1946 presented no symptoms or clinical evidence of disease and has unimpaired function of the knee. It is estimated that he received a total dosage of roentgen therapy of about 2000 r to the tumor in the upper tibia (see Fig. 205).

sarcoma (1944), expressed doubt as to the actual occurrence of this disease as a primary tumor of bone and in a personal communication stated that he felt he was correct in his impression that the only reported cases were from Memorial Hospital or inspired from that source. He felt that those lesions that were unquestionably liposarcomas might well have invaded the bone from without, while of those which appeared to be primary bone tumors none seemed to him to be unquestionable liposarcoma. The tentative recognition of these tumors was also questioned by W. G. Barnard.

Stewart, in a personal communication, expressed the conviction that these tumors are unquestionably primary rather than metastatic but freely admitted that their derivation from fat tissue could not be proven.

In the 4 cases Stewart reported (1 with Duffy) the tumors exhibited osteolytic tendencies and were quite destructive. The roentgenographic appearance did not closely resemble any other recognized primary bone sarcoma (see Figs. 206-209) though it was not incompatible with certain osteolytic forms of osteogenic sarcoma. It most closely simulated a diffuse metastatic process though in none of the cases was there any evidence of a primary cancer elsewhere, and in the case that came to autopsy careful search for a primary was unsuccessful.

Stewart has described the peculiar gross appearance, alveolar character, absence of evidence of origin from endothelioma, and xanthoma-like droplets in the histologic examinations made of these cases. He freely admits that in reporting them as liposarcomas he is "in doubtful territory" and that in none of the cases has he been able to trace the actual origin of the



FIG. 207 Liposarcoma of bone. Two separate lesions are present. These tumors proved radiosensitive but amputation was eventually required because of failure to obtain union.

tumor to fat cells. He views the evidence as entirely circumstantial: (1) the resemblance of the tumor cells to fat cells; (2) the peculiar clinical course with suggestion of multicentric origin of bone lesions such as has been observed by him in soft part liposarcomas; (3) the lack of evidence of their being metastatic from some primary epithelial tumor, and (4) lack of conformity to any of the known types of primary bone tumor.

The author personally treated 3 of Stewart's cases, was familiar with the fourth, and agrees with the viewpoint that they are examples of a distinct entity, of whose exact nature he is uncertain. Until a better explanation



FIG. 208. Liposarcoma of femur. Pathologic fracture and bulky extraosseous swelling is apparent.



FIG. 209. Liposarcoma of radius. Amputated specimen has been injected with opaque medium. Note absence of nearly the entire radius and pressure destruction of ulna in its mid-portion.

for their origin is offered it seems reasonable to classify them as liposarcomas of bone.

All of the cases have run a course that is so different from the ordinary types of bone sarcoma that one should bear this in mind in giving a prognosis. There is a tendency to appear as multiple primary tumors or to

metastasize to other bones. They are apparently radiosensitive and this includes pulmonary metastases as well as the primary tumor. One should examine the entire skeleton for evidence of other bone involvement. Amputation may prove to be curative. A guarded but not an immediately hopeless outlook is justified.

It is desirable that cases of a similar nature be reported in detail so that our knowledge of this rare tumor of bone may be increased and its true nature more fully understood.

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SECTION FOUR

Tumors Involving Bone by Extension

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INTRODUCTION TO SECTION FOUR

OWING TO THE TENDENCY OF CERTAIN PRIMARY SOFT-PART TUMORS TO erode or to actually invade bone by extension from without, it naturally follows that these tumors may present clinical and even roentgenographic features that simulate true tumors of bone. It should be understood that their proclivity for skeletal invasion is by no means constant; in some of these tumors it is actually of rare occurrence. For diagnostic purposes, much depends upon the site of origin and its propinquity to bone. The duration of the growth is another factor; early in their course these neoplasms may be devoid even of attachment to bone but as they increase in size and proceed to infiltrate adjoining tissues they may later encroach upon, and actually penetrate, the periosteum and extend into and even through the cortex to affect all the elements of bone.

The following primary soft-part tumors* are, therefore, regarded as worthy of brief consideration:

Malignant synovioma

Benign synovial tumor (giant cell tumor of tendon sheath)

Glomus tumor

Neurogenic sarcoma

Neurofibromatosis (Recklinghausen's disease) of bone

Fibrosarcoma of fascial or tendon sheath origin

Epithelial tumors may also extend to and actually penetrate the nearby bony structures. This is notably true of cancer of the oral and nasal cavities and is sometimes true of squamous carcinoma of the skin. It may also be a late sequel to cancer arising in burn scars and sinuses of long-standing osteomyelitis. Neglected breast carcinoma may erode the underlying ribs. Bladder cancer has been found to invade the pubic bone by direct extension. These tumors seldom give rise to much difficulty in diagnosis because the primary growth is generally obvious and lies in apposition to the area of destroyed bone.

29. MALIGNANT SYNOVIOMA

TUMORS WHICH ORIGINATE IN SYNOVIAL TISSUE MAY BE DIVIDED INTO TWO main groups: the benign, which resemble fibroma and xanthoma, and the malignant. The latter possess all the attributes of malignant tumors, recurring after excision, often infiltrating and destroying bone, and metastasizing to the lungs and regional lymph nodes.

The malignant synovioma is found in the region of joints, bursae, tendon sheaths, and synovial prolongations or pouches. They are rarely found in localities not known to be the site of synovial tissue.

Many names have been applied to this group of neoplasms: synovial sarcoma, perithelioma, synovial sarcomesothelioma, myxosarcoma, villous angiofibroma. Lawrence Smith, in 1927, was the first to use the term synovioma. However, since some writers have employed the term when referring to benign tumors of synovial origin, it seems wiser to adopt the qualifying term malignant to designate the tumor now under consideration.

After studying cultures in vitro of tissue from human synovial sarcoma and from normal synovial tissue from adult rats, Murray, Stout, and Poggeff concluded that the normal synovial cell is a distinct type which differs from other epithelium and from the fibroblast, and that synovial sarcoma seems to be a distinct type of neoplasm with certain similarities to the mesothelioma.

INCIDENCE

Although undoubtedly less rare than the literature would seem to indicate (up to 1945 only 104 cases have been reported, see Table XXXII), this tumor is certainly uncommon. In a three-year period, serving as surgical consultant to a large Service Command, the author encountered only 3 cases.

AGE

The disease may occur at any age. The youngest recorded case was in an infant of 9 months; the oldest, a woman of 75. More than half occur in the period from 21 to 40, the average of all cases being 31 years.

TABLE XXXII
MALIGNANT SYNOVIOMA—SUMMARY OF CASES*

No.	AUTHOR	AGE	SEX	SITE	DURATION	PRIMARY AMPUTATION	LOCAL EXTENSION	LOCAL RECURRENCE	SECONDARY AMPUTATION	METASTASIS	RESULT	TOTAL DURATION
1	Marsh	21	M	Knee	14 mos.		+	+	+	2 5 yrs	?	
2	Hannemuller	44	M	Ankle	8 mos		+	+	+		?	
3	Lejars, <i>et al.</i>	22	M	Knee	3 5 yrs		+	+	+		?	
4	Chenot, <i>et al.</i>	38	F	Foot	8 mos		+	+	+	Repeated	?	
5	Faccini	38	M	Knee	8 yrs.		+	+	+	Soon after excision	Well 1 yr.	
6	Smith	>	?	Thigh	>		+	+			Died	
7	Smith	24	F	Thigh	8 mos		+	+	+		Died	3 yrs.
8	Smith	35	M	Knee	5 mos		+	+	+	2 mos. Soon	Died	2 yrs. 5 mos.
9	Wesselin	28	M	Knee	3 mos		+	+	+		Died	Well 6 mos.
10	Tavernier	23	F	Knee	12 mos		+	+	+		?	
11	Byron	66	F	Knee	7 yrs		+	+	+	Grain	Died	9 yrs.
12	Wagner	18	F	Ankle	6 yrs		+	+	+		Well 1 yr	
13	Drex	13	F	Knee	5 yrs		+	+	+		?	
14	Sabrazas, <i>et al.</i>	18	F	Popliteal	5 yrs		+	+	+	2 5 yrs.	Died	10 yrs.
15	Sabrazas, <i>et al.</i>	30	M	Elbow	5 yrs.		+	+		Lungs, ax nodes	Died	
16	Hohenthal	22	M	Knee	3 yrs		+	+	+	Lungs, axilla	Died	8 yrs.
17	Zwahlen	22	F	Forearm	2 yrs		+	+	+	Lungs	Died	8 yrs.
18	Zwahlen	16	M	Ankle	1 yr		+	+	+	Lungs	Died	3 yrs. 5 mos.
19	Vievez	59	F	Ankle	13 yrs	Late in disease	+	+			?	
20	Bonne, <i>et al.</i>	25	F	Knee	10 mos.		+	+			Living	7 mos.
21	Holmgren, <i>et al.</i>	28	M	Knee	18 mos		+	+		Skin, ing nodes	Died	
22	Alair	21	M	Ankle	6 mos.		+	+		Lungs	Died	2 yrs. 5 mos.
23	Alair	47	M	Knee	2 yrs.		+	+		Lungs	Died	3 yrs.
24	Alair	6 mos	M	Knee	7 mos		+	+	+		Well 3.5 yrs	
25	Knott	22	F	Elbow	3 yrs	Biopsy foll by amputation	+	+	+	Shoulder, lungs	Died	10 yrs.
26	Knott	33	M	Popliteal	6 mos		+	+			Died	3 yrs
27	Knott	24	M	Foot	2.5 yrs		+	+	+	Lungs	Living 4 yrs	
28	Black	36	M	Thumb	3 yrs		+	+	+		Well 6 mos	
29	Coley, <i>et al.</i>	45	M	Finger	7 mos		+	+	+		Died	4 yrs
30	Coley, <i>et al.</i>	35	M	Sole of foot	3 yrs		+	+	+	Following radiation	Died	8 yrs. 3 mos.
31	Coley, <i>et al.</i>	22	F	Dorsum hand	7 yrs.		+	+	+		Died	
32	Coley, <i>et al.</i>	35	F	Knee	8 yrs		+	+	+	Lungs	Well 18 mos.	

TABLE XXXII (CONTINUED)

MALIGNANT SYNOVIOMA—SUMMARY OF CASES*

No.	AUTHOR	AGE	SEX	SITE	DURATION	PRIMARY AMPUTATION	LOCAL EXCISION	LOCAL RECURRENCE	SECONDARY AMPUTATION	METASTASIS	RESULT	TOTAL DURATION
33	Coley, <i>et al.</i>	12	F	Knee	1 yr.		+		Following radiation		Well 6 yrs.	
34	Coley, <i>et al.</i>	64	M	Foot	5 mos.		+				Well 3.5 yrs.	
35	Coley, <i>et al.</i>	27	M	Palm hand	6 mos.		+				Living 16 mos.	
36	Coley, <i>et al.</i>	16	M	Knee	6 mos.		+				Well 2.5 yrs.	
37	Coley, <i>et al.</i>	45	P	Great toe	1 mo.		+				Well 1.5 yrs.	
38	Coley, <i>et al.</i>	45	M	Knee	2 7/8 yrs.		+			Lungs	Recurrence	9 yrs.
39	Coley, <i>et al.</i>	70	F	Popliteal	2 yrs.		+				Persistent disease	
40	Coley, <i>et al.</i>	45	F	Dorsum foot	1 yr.		+				Died	
41	Fehr	72	F	Dorsum wrist	3 yrs.		+			Lungs, axilla	Died	7 yrs.
42	Fehr	47	M	Ankle	1 yr.		+			Lungs, axilla	Died	6 yrs.
43	Fehr	54	M	Elbow	7 yrs.		+			Lungs, brain	Died	10 yrs.
44	Fehr	18	M	Thumb	1 yr.		+				Well 1 yr.	
45	Crook Case No 24321	25	M	Knee	5 yrs.		+				?	
46	Berger	30	M	Thigh	6 mos.		+				?	
47	Berger	39	M	Thigh	6 mos.		+			Ing. nodes, abdomen, lungs	Died	1 yr.
48	Berger	26	M	Axilla	3 mos.		+			Lungs	Died	2 yrs.
49	Berger	75	F	Dorsum wrist	1 yr.		+				?	
50	Van Veenbly	51	M	Knee	9 yrs.		+				Died	10 yrs.
51	Kilgus	28	M	Hip	4 yrs.		+			Lungs	Died	7 yrs.
52	Crook Case No 24312	71	M	Popliteal	1 yr.		+			Lungs	Died	2 yrs.
53	Hatchison, <i>et al.</i>	28	P	Knee	2 yrs.		+			Lungs	Died	7 yrs.
54	Schne	32	M	Hip	3 mos.		+			Lungs	Died	5 mos.
55	Silvershield	23	M	Wrist	6 mos.		+			Lungs	Died	5 yrs.
56	Silvershield	43	M	Foot	4 yrs.		+		Soon after excision		Well 3 mos.	
57	Silvershield	53	F	Foot	4 yrs.		+			Lungs	Well 10 mos.	
58	Althin	33	M	Knee	2 yrs.		+			Lungs	Died	
59	Lechner, <i>et al.</i>	21	F	Buttock	6 yrs.		+			Lungs	Died	
60	De Santo, <i>et al.</i>	10	M	Elbow	3 yrs.		+			Ar. nodes	Living 14 mos.	
61	De Santo, <i>et al.</i>	30	M	Elbow	10 yrs.		+				Well 11 mos.	
62	De Santo, <i>et al.</i>	63	M	Elbow	20 yrs.		+				?	
63	De Santo, <i>et al.</i>	50	F	Elbow	9 mos.		+			Lungs	Died	7 yrs. 1 mos.
64	De Santo, <i>et al.</i>	26	F	Thigh	2 3/4 yrs.		Semi. ext. enclad				Well 1 yr.	
65	De Santo, <i>et al.</i>	23	M	Knee	6 mos.		+			Lungs	Living	
66	De Santo, <i>et al.</i>	12	F	Knee	6 yrs.		Twice explored			Lungs	Well 9 mos.	
67	De Santo, <i>et al.</i>	24	F	Knee	6 yrs.		+			Lungs	Died	16 yrs.
68	De Santo, <i>et al.</i>	34	F	Wrist	10 yrs.		+			Lungs	Died	11 yrs.
69	De Santo, <i>et al.</i>	35	M	Knee	8 yrs.		+			Generalized; lungs	Well 18 mos.	
70	De Santo, <i>et al.</i>	25	M	Knee	6 mos.		+				Well 1 yr.	
71	De Santo, <i>et al.</i>	32	F	Elbow	1 mo.		+					
72	De Santo, <i>et al.</i>	45	M	Popliteal			+					

73	De Santo, <i>et al</i>	46	M	Popliteal	1 mo	+	+	9 mos	+	Lungs	Well 1 yr Died	3 yrs. 5 mos.
74	De Santo, <i>et al</i>	40	M	Proximal lower leg	2 yrs	+	+			Lungs, bones, skin, abdomen	Died	1 yr. 5 mos
75	De Santo, <i>et al</i>	45	M	Elbow	1 mo	+	+				Died	4 yrs. 5 mos.
76	Jaffe, <i>et al</i>	28	M	Knee	II 5 yrs	+	+				Well 3 5 yrs.	
77	Jaffe, <i>et al</i>	24	M	Foot	2 yrs	+	+	13 mos	+		Died	
78	Jaffe, <i>et al</i>	20	F	Knee	3 yrs	+	+			Lungs	Died	9 mos.
79	Jaffe, <i>et al</i>	15	M	Ankle	3 yrs	+	+	2 mos.	+	Lungs	Died	3 yrs.
80	Votta	63	M	Knee	3 mos	+	+	6 mos	+	Ing. nodes, lungs	Died	5 yrs.
81	Fisher	20	F	Popliteal	Months	+	+	Few mos			Well 7 yrs	
82	Briggs	17	F	Ankle	4 mos	+	+				Died	
83	Briggs	45	F	Knee	4 yrs.	+	+	2 5 yrs	+	Ing. nodes lungs	Died	8 yrs.
84	Briggs	30	F	Sole of foot		+	+				Well 1 5 yrs	
85	Briggs	II	F	Ankle	2 5 yrs.	+	Exploratory dissection				Well 2 5 yrs.	
86	Briggs	45	M	Thigh	3 yrs	+	+				Well 4 5 yrs.	
87	Briggs	17	M	Elbow	4 mos.	+	+			Lungs	Died	11 yrs.
88	Briggs	35	F	Knee	7 yrs	+	+			Ing. nodes, lungs	Died	1 yr.
89	Briggs	25	M	Popliteal	3 mos.	+	+	12 mos	+	Lungs	Recurrence Well 1.5 yrs Living 5 mos.	
90	Briggs	27	M	Popliteal	5 weeks	+	+				?	
91	Snyder	35	F	Knee	2 yrs.	+	+			Ing. and iliac lymph nodes	Well 2 yrs. Living 1 yr.	
92	Stanford, <i>et al</i>	16	M	Knee	3 mos.	+	+			Diffuse nodes and abdomen	Operative ileath	5 yrs
93	Eveleth, <i>et al</i>	61	F	Knee	4 yrs.	+	+				Well 8 yrs. 8 mos	5 yrs. 4 mos
94	Lazarus, <i>et al</i>	30	M	Hand	2 2 yrs.	+	+			Lungs	Well 15 mos	
95	Lazarus, <i>et al</i>	47	F	Knee	9 mos	+	+				Died	
96	Columbia Univ.	37	F	Popliteal	5 yrs	Exploratory dissection	+				Well 3, 4 yrs Living 3 mos. Living 4 mos Living 16 mos.	6 yrs.
97	Columbia Univ.	27	M	Elbow	4 yrs	+	+				Well 15 mos	
98	Columbia Univ.	19	M	Groin	15 mos	+	Exploratory dissection				Died	
99	Columbia Univ.	44	M	Thigh	1 yr.	+	+				Well 3, 4 yrs Living 3 mos. Living 4 mos Living 16 mos.	
100	Columbia Univ.	10	M	Groin	8 mos	+	+				Well 3, 4 yrs Living 3 mos. Living 4 mos Living 16 mos.	
101	Columbia Univ.	5	M	Knee	3 mos	+	+				Well 3, 4 yrs Living 3 mos. Living 4 mos Living 16 mos.	
102	Columbia Univ.	II	M	Knee	3 mos	+	+				Well 3, 4 yrs Living 3 mos. Living 4 mos Living 16 mos.	
103	Columbia Univ.	29	F	Foot	5 yrs	+	+				Well 3, 4 yrs Living 3 mos. Living 4 mos Living 16 mos.	
104	Columbia Univ.	31	F	Popliteal	8 mos	+	+				Well 3, 4 yrs Living 3 mos. Living 4 mos Living 16 mos.	

• Collected from the literature by HAGENSKEN, C. II., and STROUT, A. P. (Synovial sarcoma, *Ann. Surg.* 120 826, 1944), with additions from Columbia University and the Presbyterian Hospital.

The following figures show the distribution of 103 cases according to decades:

<i>Decade</i>	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
<i>Cases</i>	4	14	39	19	16	4	5	2

LOCATION

The location of the 104 cases collected from the literature by Haagensen and Stout reveals the following incidence; more than 75 per cent are situated in the knee, foot, ankle, or elbow:

Knee	49	Thigh	7	Finger	2	Forearm	1
Foot	10	Wrist	4	Hip	2	Buttock	1
Ankle	9	Hand	3	Groin	2	Leg	1
Elbow	9	Thumb	2	Axilla	1	Toe	1

CLINICAL FEATURES

Pain is the presenting symptom in about 50 per cent of cases. Swelling in the form of a noticeable lump is an almost universal finding but it has often been present for years and it is believed that there may be a long latent period before the tumor takes on truly malignant features and commences to increase rapidly in size. Trauma has been a feature mentioned in many of the case histories; while its relationship cannot be denied absolutely, it is certainly questionable.

Bone changes have not been described in most case reports. We have observed a considerable number in which the adjacent bones have been invaded, eroded, and even extensively destroyed (see Figs. 210 and 211). Destructive changes may closely resemble osteolytic osteogenic sarcoma and, in 1 case involving the ankle, joint tuberculosis was closely simulated on roentgenographic examination (see Fig. 212).

ROENTGENOGRAPHIC APPEARANCE

Films of the affected part, taken with special reference to soft-tissue detail, may disclose the tumor despite absence of any bone involvement. Examination should always include anteroposterior and lateral chest films to rule out the presence of pulmonary metastasis.

Lewis has contributed to our knowledge of the roentgenographic appearance of these tumors. In a detailed study of the films of 10 cases, he found 4 which presented a more characteristic appearance and he concluded that in one fourth of these tumors one can make a provisional diagnosis of synovioma. He states that when, in addition to the finding of a rounded, sometimes lobulated, sharply defined soft-tissue tumor mass, there are scattered irregular deposits of calcium within this mass, one is justified in making a provisional diagnosis of synovioma.

In deeply situated tumors planographic exposures may give additional information.



FIG. 210. Malignant synovioma of knee showing tumor closely adherent to the femur and resembling grossly the periosteal form of osteogenic sarcoma. (Letterman General Hospital.)



FIG. 211. Malignant synovioma of astragalo-scapoid joint. The spotty calcification in the soft tissues is especially marked in this case and the location is unusual. It was readily mistaken for a primary bone tumor. (Station Hospital, Fort Worth Army Air Base)

DIAGNOSIS

It is surprising how seldom the correct diagnosis is made until the sections of tissue reach the pathology laboratory. The tumor is often excised



FIG. 212. Malignant synovioma of ankle with invasion and destruction of bone. This case was referred with a tentative diagnosis of tuberculosis. Though it does not produce bone, this tumor not infrequently destroys it. (Army & Navy General Hospital.)

in the office or outpatient clinic and the surgeon, unaware of its possible serious nature, fails to do a wide and radical extirpation. Soft-part growths for which it may be mistaken include ganglion, fibroma, cyst, xanthoma, etc.

A soft-part tumor in the hand or foot, or in the region about the joints, bursae, or tendon sheaths, should be regarded as a potential synovioma until proven otherwise by microscopic study. If it is movable and capable of complete excision it should not be biopsied but should be completely and widely removed. Aspiration biopsy, however, is permissible.

GROSS APPEARANCE

The gross appearance of these tumors is variable. Some are whitish, others a bluish gray or pink color on section. Some are well encapsulated, bean- or pea-like, while others infiltrate surrounding tissues widely. They tend to be vascular, and in large growths there may be areas of cystic degeneration with viscid mucinous material.

TREATMENT

A localized soft-part tumor near a joint in the hand or foot or in a locality where the presence of synovial tissue is to be expected should be regarded with respect and widely and cleanly excised, and under no circumstances should a removable mass be biopsied. Complete and thorough removal

is too seldom accomplished at the outset; the recurrences that follow are seldom capable of successful local removal so that amputation is then required and this is generally carried out too late to save the life of the patient. It can be stated with certainty that once a synovioma has extended to bone, as evidenced by roentgenographic appearance, an amputation should be performed promptly in preference to any attempt at local excision. In our experience where bone involvement has occurred the ultimate outlook has been extremely unfavorable.

Amputation as an early primary procedure (performed in only 4 of the 104 collected cases previously referred to) has apparently not had sufficient trial. In fact the surgical treatment of synovioma appears to have been too limited in its scope at first and, when radical measures have finally been undertaken, it has been too late to prevent dissemination of the disease.

Radiation therapy has not been effective and is considered inadvisable, for this tumor is definitely radioresistant. Since it has a marked tendency to metastasize (though in some instances years elapse after the primary tumor has been removed before metastatic foci are recognized), every case should be followed for an indefinite period. If there are any symptoms referable to the lungs, chest films are in order.

Inoperable tumors pose an almost insoluble problem; roentgen therapy may exert slight growth restraint. Some of these cases may require chor-dotomy.

The wisdom of a groin or axillary dissection as an additional measure after excision or amputation is open to argument. In about one-fourth of the cases in which the site of metastasis is recorded there was regional node involvement; yet in nearly all, the lungs also were affected. It does not seem, therefore, that routine lymph-node dissection is warranted.

PROGNOSIS

The extremely unfavorable outlook in this disease is perhaps somewhat tempered by the unusual survival period which may extend from five to fifteen years following the first symptoms. It is possible that the high mortality is attributable to two factors: (1) the tumors are usually painless at first so that the patient is slow to consult a physician; (2) on first examination their removal seems disarmingly simple so that it is carried out incompletely. A recurrence follows which is generally subjected to a second excision and amputation is finally resorted to when it is too late to prevent pulmonary metastases.

One case is recalled in which four such attempts at excision were made, followed by two thigh amputations; another patient underwent three unsuccessful attempts at local removal and, when first seen by the author, presented pulmonary metastases and bulky recurrent disease surrounding the supracondylar area.

30. BENIGN SYNOVIAL TUMOR

(Xanthoma or Giant Cell Tumor of Tendon Sheath Origin)

GIANT CELL TUMOR OF TENDON SHEATH (XANTHOMA) IS THE MOST common of all benign tumors arising from elements of synovial origin. It occurs as circumscribed, sometimes lobulated, pea- or bean-sized

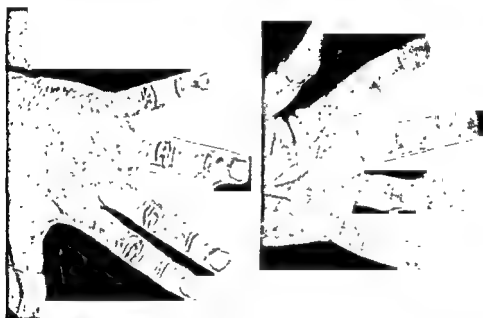


FIG. 213. Benign synovial tumor.

masses situated most often along the flexor tendons of the fingers (see Fig 213) and less frequently in the wrist or hand. These xanthomas are firm, encapsulated, and of slow growth. On section they present a characteristic yellowish or brownish appearance.

Geschickter and Copeland believe that giant cell tumors of tendon sheaths are derived from sesamoid bones. These observers maintain that the location of these tumors invariably coincides with sites of these bones and that microscopic examination usually reveals some trace of the original structure of sesamoid bones. They therefore contend that these giant cell tumors are erroneously termed xanthomas and are not soft-part neoplasms

but actually tumors of sesamoid bones. So far as we are aware, this ingenious theory has not been confirmed by other investigators.

The roentgenographic appearance in most instances is that of a soft-tissue shadow with no alteration in the bone adjacent to the tumor. Rarely one may find changes in the bone attributable to pressure of the overlying tumor. In such instances it is theoretically possible that a periosteal fibrosarcoma might be suspected, although the outline of the defect in the bone is smooth and does not suggest actual invasion. In 1 such case we were able to enucleate the tumor with ease. There was no indication that it had extended into the bone itself. The exceeding rarity of a primary sarcoma of a finger bone should always be borne in mind, and amputation should be withheld until histologic examination has established the presence of an undoubted malignant lesion.

Aside from the annoyance or occasional interference with finger or hand function caused by their presence, these tumors are not only benign but cause only mild, transitory symptoms. If not completely excised they tend to recur locally but they do not metastasize and never call for radical treatment. The only lesion with which they may be confused is the malignant synovioma which is seen very rarely in the hand or fingers. If we adhere to the practice of a thorough removal of every tumor of the tendon sheath, followed by a careful study of the specimen in the pathology laboratory, little difficulty will be encountered in distinguishing between the true synovial sarcoma, or synovioma, and the xanthoma. The striking feature of the histologic picture is the presence of xanthoma cells or "foam cells" which lie in a fibrous stroma. These cells lack atypism and hyperchromatism indicative of malignancy.

The treatment should consist in a careful excision of the entire tumor in one piece. The use of a tourniquet to obtain a bloodless field will be found helpful.

31. GLOMUS TUMOR OF BONE

FOR OVER TWENTY YEARS FOLLOWING MASSON'S ORIGINAL ARTICLE, TUMORS of the neuromyoarterial glomus have been recognized. While formerly considered extremely rare, they are now seen and described with greater frequency. Approximately half of the cases encountered at Memorial Hospital by Adair involved the nail bed; the rest were distributed on the hands, arms, and legs but none were situated on the trunk or head.

The most outstanding clinical characteristic is excruciating tenderness and pain upon the most trivial contacts.

In appearance the lesion resembles an intradermal neurofibroma or a small hemangioma. It is slightly elevated, rounded, and has a reddish or violaceous tint. In size it varies from 0.8 to 1.0 cm. in diameter. Its nature is benign.

To the author's knowledge, only a single report has ever been made of the occurrence of this tumor entirely within the confines of bone. This case, described by Iglesias de la Torre, Gomez-Camejo, and Palacios, was found to be entirely within the bone of the terminal phalanx of a finger. Stout, in a personal communication, relates having examined an almost identical case, similarly situated, in which the typical symptom of paroxysmal pain existed but the roentgenogram revealed multiple areas of rarefaction resembling central chondroma or giant cell tumor of the phalanx.

The treatment of these tumors in bone, as in the usual location in skin, is surgical extirpation.

32. NEUROGENIC SARCOMA

DEEPLY SITUATED NEUROGENIC SARCOMAS MAY BY THEIR PROXIMITY TO bone give the clinical impression that they actually arise from periosteum and are therefore periosteal fibrosarcomas; it may be difficult even for the pathologist to decide this question after examination of the amputated limb. In the ordinary case of neurogenic sarcoma that is closely attached to bone there is no actual invasion of the cortex and the roentgenographic appearance reveals no osseous changes. In bulky, long-standing tumors, on the other hand, there may be bone changes due to pressure of the overlying tumors or even extension of the process into the bone, such as we occasionally see in malignant synovioma. With this situation a pre-operative diagnosis can be made only by conjecture. Nevertheless the distinction is rather an academic one because in either case treatment involves surgical extirpation and this nearly always means an amputation.

33. NEUROFIBROMATOSIS OF BONE (RECKLINGHAUSEN'S DISEASE)

BONE CHANGES IN CASES OF TYPICAL RECKLINGHAUSEN'S DISEASE HAVE been recognized since 1901 and numerous papers have been written emphasizing the skeletal alterations which are estimated to occur in 7 per cent of the cases. Lehman and Brooks, in 1924, classified these bone changes as follows: (1) sclerosis, (2) abnormalities of growth of individual bones associated with elephantiasis, and (3) irregularity in the outline of bones ranging from central to subperiosteal tumors.

The presence of nerve tissue in bone, both compact and cancellous, has been known for more than fifty years. Kölliker describes the nerve supply of bone in some detail and acknowledges contributions of the earlier histologists who made similar studies. Both sympathetic and cerebrospinal nerve fibers are found in periosteum, and extremely small trunks have been found to accompany the nutrient vessels. There has not been presented unequivocal proof that the marrow of bone is supplied with nerve fibers; however, Peers has reported a perineural fibroblastoma in the marrow of the ulna and DeSanto and Burgess have described the finding of a neurilemmoma in bone. According to Friedman's deduction, the bone changes are not due to neurofibromatous invasion of bone but to neurofibromatous tissue arising within the bone itself.

34. FIBROSARCOMA OF FASCIAL OR TENDON ORIGIN

A SITUATION SIMILAR TO THAT OF NEUROGENIC SARCOMA OR NEUROFIBROMATOSIS of bone arises infrequently in cases of fibrosarcoma of deep fascial origin, and more often in those arising from tendinous insertions. These may be difficult to distinguish from neurogenic sarcoma or from periosteal fibrosarcoma. They tend to run a less malignant course and may yield to radical surgery with a somewhat better prognosis than is the case in either of the other tumors. In a number of instances our pathologists have stated that the histologic picture gave assurance that while the tumor would recur locally if not widely excised, it would be extremely unlikely for it to metastasize in its present form.

In the past an occasional brilliant response to combined interstitial and external radiation therapy has been observed although a location suitable for this method is not often present. In general, we prefer surgery and have attempted to avoid immediate amputation. We have utilized segmental resection or local removal of the affected area of bone as an alternative (see Fig. 284, p. 492). External irradiation alone is not advisable as these tumors are not radiosensitive.

35. CARCINOMA

IT MUST BE UNDERSTOOD THAT ANY CARCINOMA ARISING IN STRUCTURES adjacent to bone may invade the latter by direct extension, e.g., involvement of the mandible is not uncommon in extensive carcinoma of the buccal cavity, floor of the mouth, or in some cases, of the lip. Mammary cancer may invade the ribs by direct extension from the primary growth. Occasionally neglected cancer of the bladder may affect the contiguous portions of the bony pelvis; and tumors of the nasopharynx and antrum may erode the adjacent superior maxilla, ethmoid and nasal bones.

These situations, however, present little difficulty in making a diagnosis since they are hardly ever confused with primary neoplasms of bone.

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SECTION FIVE

Metastatic Tumor Involving Bone

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36. METASTATIC CARCINOMA

SECONDARY MALIGNANT DEPOSITS IN BONE ARE NUMERICALLY FAR more important than are primary sarcomas. Their frequency is not generally appreciated, principally because of the lack of routine skeletal examination. Kauffmann found at autopsy that roughly one half of all prostatic and two-thirds of all breast cancers showed bone metastases. Accor Kitain of the Lubarsch Institute, Berlin, 10 per cent of all types of carcinoma develop skeletal metastases.

Spread of malignant disease to bone can occur as a result of direct extension of an overlying soft-tissue tumor. True metastasis can take place through the blood stream or by retrograde lymphatic channels. The latter route may give rise to deposits in any of the bones; however, it is not easy to find them below the elbows or knees and rarely are they seen in the hands or feet. Where retrograde lymphatic extension is the route, metastases near the primary growth are naturally more liable to invasion. In the case of mammary cancer the ribs, thoracic spine, and skull are favored sites, while in prostatic cancer the sacrum, pelvis, and lumbar spine are commonly affected.

There is a great variation in the frequency with which carcinomas of the same or different organs metastasize to bone. Those which have this tendency are termed *ossophile* while those which do not are called *ossophobe*.

OSSOPHILE CARCINOMAS

Breast
Prostate
Thyroid
Kidney
Lung

OSSOPHOBIC CARCINOMAS

Skin
Oral cavity
Esophagus
Cervix
Stomach
Colon

Borak lays down the first fundamental principle of the biology of metastasis as follows: very slow-growing carcinomas of certain histological structure metastasize to bone without affecting the viscera. The first principle Borak cites as follows: the spine, pelvis, and upper femur are especially prone, while below the elbows and knees it is most uncommon to find metastases. Borak explains this by assuming that in parts

skeleton which are used less dynamically, e.g., the spine, there are apparently better conditions for retention of the carcinoma cells which are carried to it through the blood stream. In these less used parts of the skeleton the blood stream flows more slowly and permits easier retention in the bone marrow to which the tumor cells are borne. As would be anticipated, most bone metastases begin in the spongiosa and are therefore marrow metastases. Cortical lesions are infrequent although as a central area progresses it extends to invade cortical bone.

OSTEOBLASTIC METASTASES

It should be understood that bone formation seen in osteoblastic metastatic foci is not a result of metaplasia of tumor cells but arises from the stroma of the carcinoma or as a reactive phenomenon on the part of the osteoblasts responding to the stimulus to repair destroyed bone. This is also seen in certain primary bone sarcomas, notably osteogenic sarcoma, where the wedge-shaped zone of reactive bone about the margin of the advancing tumor has been described by Codman and termed by others *Codman's triangle*. Osteoblastic metastases are most often seen in prostatic carcinoma, especially in the spine and pelvis. They may be found in association with osteolytic areas in the same patient. When this occurs the areas in the extremity bones or the skull are generally osteolytic.

Osteoblastic reaction is seen after roentgen therapy even in cases in which the areas prior to treatment were purely osteolytic, provided the carcinoma is radiosensitive. In such cases the osteoblastic reaction implies destruction of carcinoma cells and *restitutio ad integrum*.

OSTEOLYTIC METASTASES

Osteolytic metastases are frequently found in cases of renal and thyroid carcinoma. In the former they are spotty and the outline of the bone appears to be erased; in the latter there is an expansile tendency (*cystic type*, Kienboeck; *soap-bubble type*, Schinz). Such areas, when solitary, may resemble cystic disease or even giant cell tumor.

It can be shown that the prostatic and breast metastases are very often osteoblastic whereas those of thyroid and renal origin are extremely rarely so; the latter are nearly always osteolytic. Moreover the prostatic and breast metastases are most frequent in spine and pelvis while those of the kidney and thyroid not infrequently affect bones of the extremities.

	BREAST AND PROSTATE	KIDNEY AND THYROID
<i>Osteoblastic</i>	Frequent	Rare
<i>Osteolytic</i>	Rare	Frequent
<i>Spine, pelvis</i>	Common	Less common
<i>Extremities</i>	Less common	Common
<i>Multiple</i>	Common	Solitary

CARCINOMA OF THE BREAST

This organ is probably the most important source of osseous metastases, which appear in from 25 to 35 per cent of all cases of breast carcinoma.



FIG. 214 Osteoblastic metastatic carcinoma of breast showing unusual distribution of lesions.

At times they give rise to symptoms and are discovered even before the lump in the breast is noted. On the other hand they may appear at any time after radical mastectomy, *i.e.*, from a few weeks to several years. Bone metastasis occurs most often in those cases that fall into Portmann's clinical grades II and III. Undoubtedly, a routine roentgenographic examination of the skeleton would disclose a much higher frequency rate of osseous deposits than is generally realized. Despite such examination, early spread to bone is not easily verified on the films; this is especially true where spine and ribs are concerned. By the time definite complaints of pain are made,

there is usually sufficient alteration in bone architecture to be detectable on the roentgenograms, thus permitting at least a presumptive diagnosis.

Wolff claims that if all cases of skeletal metastasis were subjected suffi-



FIG. 215. Carcinoma of the breast with "solitary" metastasis to the humerus. A radical mastectomy had been done and no nodes were found involved. Roentgenograms of entire skeleton including chest failed to reveal any other evidence of disease.



FIG. 216. Metastatic carcinoma of breast—a rather unusual location.

ciently early to roentgenographic examination and if the areas of neoplastic involvement were large enough, the lesion would always prove to be osteolytic. According to Hellner and Axhausen, microscopically every bone tumor, either primary or metastatic, begins as an osteolytic type. Wolff further considers that osteoblastic predominance in a lesion indicates slow growth both in primary and metastatic tumors. This view is borne out by our experience at Memorial Hospital. Cases are seen in which there are both osteoblastic and osteolytic areas combined (see Fig. 214).

Next to cancer of the prostate, cancer of the breast is the most frequent source of osteoblastic metastases. This does not mean, however, that most mammary metastases are osteoblastic, for the osteolytic variety predominates (see Figs. 215-217). Progress is slower and survival is prolonged

in the osteoblastic form, some patients living from three to four years. Generally it is noted that the osteolytic type gives rise to much more extensive areas, which often involve the entire thickness of the cortex and



FIG. 217. Metastasis to os calcis from mammary carcinoma. A very unusual site for metastatic deposits.

present as palpable tumors. The osteoblastic form remains more localized, is often not recognizable save on roentgenographic study, and is seldom the cause of pathologic fracture.

Numerically there is also great variation in individual cases, ranging from infrequent or even solitary metastases to widespread dissemination throughout many bones. In our experience the more diffusely scattered the lesions the more apt they are to prove radiosensitive and to be benefited by the removal of ovarian hormones.

Ovarian sterilization has been extensively employed in recent years for metastatic breast cancer. It is now known that local and visceral involvement is but little affected and that the striking benefits are seen in cases with bone invasion.

That the beneficial factor is the withdrawal of the ovarian hormone seems unquestioned; thus is explained the fact that areas of metastasis in bones that have not been exposed to roentgen rays have shown pronounced regression following ovarian castration.

As would be expected, sterilization is mainly effective in young patients. Dramatic results are seldom seen in patients who have already passed the menopause.

Beneficial results include relief from pain; this is noted rather promptly and in some cases is sustained over a period of many months or even several years. Hypnotics and sedatives can often be discarded. Areas of bone erosion or destruction may be partially or completely regenerated and pathologic fracture be postponed or prevented; general improvement is

manifested by better appetite; weight is gained and physical status enhanced so that activity and usefulness are restored with a distinct improvement in morale.



FIG. 218. A, Metastatic mammary cancer. Note osteolytic areas diffusely scattered throughout pelvic girdle and upper femora; B, same case following roentgen castration. Note replacement of osteolytic areas by marked osteoblastic production.

METHOD OF ROENTGEN STERILIZATION

Using anterior and posterior fields, 15 x 15 cm., over the lower abdomen and lumbosacral areas, doses of 200 r are delivered to each field in rotation, using 0.5 mm. of copper and 1.0 mm. of aluminum, 200 kv. and 50 cm. TSD, until 2400 r have been administered (600 to each of the four portals). During treatment, measures to combat systemic effects of radiation are advisable, *e.g.*, high fluid intake, large doses of vitamin-B complex, large quantities of fruit juices, and amphetamine or dextro-desoxyephedrine is given three times a day (maximum total daily dose of 30 mg. of amphetamine or 20 mg. of dextro-desoxyephedrine). These drugs are given orally and are not habit-forming if administration is stopped when radiation therapy is terminated.

About a third of the cases of breast cancer with osseous metastases are benefited by roentgen sterilization, and since the favorable responses are so striking it is worthwhile to resort to it except in extremely far-advanced and cachectic cases (see Fig. 218).

It becomes important for every patient who has had breast cancer to have a careful skeletal examination at intervals of four to six months so that osseous foci can be detected early and sterilization be carried out promptly. There are no overruling contraindications to its use provided there is a reasonable prospect of benefit. This is not true of soft-part metastases, and it is not justifiable to add to the patient with metastatic breast cancer the burden of coping with a premature menopause.

It is not as yet clearly established whether or not sterilization actually prolongs life. It has seemed to do so in some of our personally treated cases although this is an extremely difficult assumption to prove.



FIG. 219. Bone metastases from gastric cancer.

In a small series of cases Treves has obtained control of bone metastases from carcinoma of the male breast following surgical castration.

Recently extensive trials have been made of testosterone propionate in the treatment of metastases from carcinoma of the female breast. It is too early for final evaluation of the effectiveness of this type of therapy. In general, the results with soft-part metastases have been disappointing. Results of the treatment of bone metastases, on the other hand, have been more encouraging. A significant proportion of the patients experience relief of symptoms and arrest of the progress of the disease for a number of months, and in an occasional favorable case the improvement may continue for two or more years. There is usually an increase in the formation of new bone in the metastatic areas associated with a rise in the serum alkaline phosphatase early in the course of treatment, and in favorable cases there may be a restoration of normal texture. The method is not entirely safe, as an occasional patient experiences an acute exacerbation of the disease, with rapid osteolysis and a dangerous hypercalcemia.

CARCINOMA OF GASTROINTESTINAL TRACT

While skeletal metastasis from primary tumors of the gastrointestinal tract are uncommon, this source must be considered when bone lesions are met and an undetermined primary carcinoma is suspected (see Fig. 219).

In a series of more than 12,000 autopsies, Müller found 567 instances of gastrointestinal tract carcinoma with bone metastases as shown in the accompanying table.

TABLE XXXIII
BONE METASTASIS WITH PRIMARY GASTROINTESTINAL CARCINOMA

SITUATION OF PRIMARY CARCINOMA	NO. OF CASES	CASES WITH METASTASIS TO BONE No.	PERCENTAGE
Stomach	309	8	2.58
Oesophagus	101	7	6.93
Rectum	57	8	10.52
Gall bladder	56	2	3.57
Pancreas	19	4	21.05
Liver	15	3	20.00
Pharynx	10	2	20.00

Most writers report an incidence of bone metastasis in gastrointestinal cancer of from 1 to 3 per cent; however, if one considers Ghormley and Valls' studies from clinical rather than postmortem sources, it appears that the incidence is only from 0.2 to 0.5 per cent. Their analysis of metastatic growths in bone encountered in cases of gastrointestinal cancer at Mayo Clinic from 1922 to 1936 is as shown in Table XXXIV.

TABLE XXXIV
BONE METASTASIS WITH PRIMARY SOFT-PART CARCINOMA*

PRIMARY GROWTHS		SECONDARY GROWTHS						INCIDENCE OF METASTASIS TO BONE FROM ALL CARCINOMATA OF THE INDICATED ORGANS (PERCENTAGE)	
		SITUATIONS							No
		Spine	Pelvis	Ribs	Long Bones	Sternum	Scapula		
Situation	No.								
Oesophagus	1			1			1	0.2	
Stomach	12	6	3	5	2	1	17	0.2	
Small bowel	1	1					1 ^b		
Colon	3	1	1	1			3		
Sigmoid	3	2		2	1		5	0.3	
Rectosigmoid	4	3	2				5		
Rectum	19	6	8	1	3		19	0.5	
Totals	43	19	14	10	6	1	51		

* GHORMLEY, R. K. and VALLS, J. E. Metastasis to bone from carcinoma of gastrointestinal tract. *J. Bone & Joint Surg.* 21: 74, 1939

^b One case of metastasis from carcinoma of the small bowel, this primary growth is rare

CARCINOMA OF THE PROSTATE

Cancer of the prostate may arise insidiously and spread to the pelvic bones and spine causing dull, aching pain before there are any noteworthy symptoms referable to the primary growth. The relative increase in acid phosphatase which accompanies bone metastases from this organ is a reliable indication and its importance has been emphasized in Chapter 5.

page 59. Areas of increased density in the bones of the spine and pelvis, femora and skull (see Figs. 220 and 221) in a male patient within the cancer age should suggest the probability of carcinoma of the prostate, and



FIG. 220. Osteoblastic metastatic carcinoma of pelvis from primary carcinoma of the prostate.

clinical and laboratory studies should be made without delay. In advanced cases the bones are diffusely mottled with small areas of increased density which give a "snowflake" appearance that is characteristic.

The effectiveness of endocrine treatment of metastasizing carcinoma of the prostate has been well established by the work of numerous investigators. Either surgical castration or the administration of estrogens is effective in 90 per cent of the cases, and both bone and soft-part metastases are controlled. The institution of either treatment is followed promptly by a great increase in the degree of osteoplasia of the metastatic areas in bone. Later the areas may resume an almost normal appearance. While the majority of the patients show evidence of relapse in eight to twelve months, a considerable number remain free of active disease for from two to three years. A few cases have been reported who died of other causes several years after the institution of endocrine therapy in whom careful autopsy failed to show the presence of any residual primary or metastatic cancer. In these rare cases a true cure appears to have been brought about by endocrine therapy.

CARCINOMA OF THE THYROID

Cancer of the thyroid may give rise to bone lesions especially in the skull, spine, and pelvis. We have been impressed with the frequency with which the

ilium has been affected in these cases. Such tumors are bulky, osteolytic, destroying a large portion of the bone and producing a tumor that is readily palpable (see Fig. 222). In the past there has been confusion



FIG. 221. Metastatic carcinoma of prostate. Note resemblance to primary bone tumor despite location in midshaft.

regarding the occurrence of osseous metastases following the removal of thyroid tumors which have been considered histologically benign. These are now believed to be malignant despite the fact that the histologic features of the primary growth are those of a benign rather than a malignant process. In such cases a lapse of several years between thyroidectomy and the discovery of bone metastases is not unusual (see Figs. 223 and 224).

Outerbridge found in a series of 2268 thyroidectomies in Toronto General Hospital 60 instances of carcinoma of which 24 were diagnosed as malignant adenoma, 5 of the latter had metastases to bone.

Cohnheim, in 1876, called the condition "benign metastasizing goiter." In 1926, Simpson recorded 3 instances of so-called "benign metastasizing

Ewing has stated that metastases from this type of tumor usually present a microscopic structure of more adult type than the original tumor, also that the character of the tissue found within the metastatic nodule



FIG. 224. Carcinoma of thyroid metastatic to mandible. In this case the interval between thyroidectomy and discovery of the metastasis was seven years. Deposits were also noted in the lung and femur.

always corresponds in morphology to some portion of the primary tumor.

Graham considers that the most constant single criterion of epithelial malignancy of thyroid tumors is invasion of blood vessels. According to Rienhoff, metastases from normal thyroid do not occur, and this statement is generally concurred in by most pathologists.

Outerbridge recommends complete excision of the primary malignant adenoma and the metastases as promptly as possible. When these are skeletal such a procedure is seldom possible. However, if the primary tumor has not been excised when the osseous metastases are discovered, it should be removed because if left it will continue to disseminate emboli. Roentgen therapy has proved of distinct value in the treatment of bone deposits in this disease. One of our cases with foci in the ilium and spine first noted thirteen years after removal of the thyroid nodule has remained well and free of evidence of disease eight years after the administration of roentgen therapy.

Bone lesions that are purely osteolytic at the outset and have been given radiation therapy may exhibit marked osteoblastic reparative tendencies, evidence of a favorable response.

A recent trend which warrants considerable future development is the use of radioactive iodine in the treatment of thyroid cancer metastases to bone. Tentatively, it would appear that metastatic lesions that produce colloid will, in some instances, pick up radioactive iodine selectively. This can be determined by administering a small tracer dose of the substance and measuring its distribution with the Geiger counter. Suitable cases may

then be given therapeutic doses in amounts and at intervals dependent upon the individual response.

Encouraging early results have been obtained to date but the method



FIG. 225. Metastatic hypernephroma.



FIG. 226. Metastatic renal carcinoma (clear cell type). Note resemblance to angioma of bone.

is too new to permit of any observations over a prolonged period or definite conclusions as to its ultimate value.

HYPERNEPHROMA

Hypernephroma is frequently complicated by skeletal metastases which are few in number or even solitary. Since they may attract attention before the primary tumor is discovered there is a possibility of mistaking them for primary sarcoma. Metastases are osteolytic, often bulky, and may reach considerable size (see Fig. 225).

CARCINOMA OF KIDNEY

Ewing has pointed out the fact, which coincides with our observation, that while bone metastases from tumors of the kidney region have usually been termed hypernephroma on the assumption that they were derived

from adrenal rests most of them are probably clear cell renal carcinomas. The frequency with which these tumors metastasize to bone is well recognized.



FIG. 227. Solitary metastatic carcinoma of renal origin involving the femoral shaft.

They usually occur in the long bones, skull, spine, ribs, and scapula. Their importance to us lies in the frequency with which the secondary bone lesion gives rise to the first symptom and resembles a primary tumor or some other bone disease. The primary renal tumor may be discovered only late in the course of the disease or perhaps at necropsy (see Figs. 226 and 227).

Metastasis to bone from Wilm's embryonal tumor of the kidney is exceedingly rare in our experience. However, one case in which the femur was the site of the secondary growth is illustrated in Figure 228.

CARCINOMA OF BLADDER

Cancer in this locality seldom metastasizes to bone but the disease may spread to adjacent portions of the bony pelvis by extension (see Fig. 229).

CANCER OF CERVIX, UTERUS, ETC.

Carcinoma of the female generative organs is seldom associated with metastasis to bone. However, Figure 230 shows an instance of spread from a

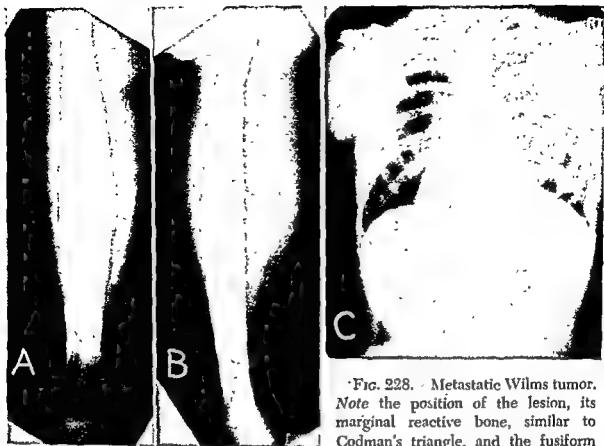


FIG. 228. Metastatic Wilms tumor. Note the position of the lesion, its marginal reactive bone, similar to Codman's triangle, and the fusiform expansion of the shaft. Note also the

chest film which shows diffuse pulmonary metastasis on the left side.



FIG. 229. Carcinoma of bladder with infiltration of pubic bone.

cancer of the cervix to the humerus causing symptoms which were at first interpreted as being due to a subdeltoid bursitis.



FIG. 230. A, Patient with uterine carcinoma with complaint of pain in the shoulder. Note the presence of calcified bursitis. B, Same case six months later after treatment of the bursitis by novocaine injections. Pain persisted. Now obvious metastatic disease with pathologic fracture.

TERATOMA TESTIS

Malignant testicular tumors rarely spread to bone; however an example of such occurrence is shown in Figure 231.

BRONCHOGENIC CARCINOMA

Bronchogenic carcinoma gives rise to bone metastases which are characterized by increased radiolucency with little tendency to produce reactive bone (see Figs. 232 and 233). Formerly these tumors occurring in bone were incorrectly interpreted as primary; the lung tumors were regarded as pulmonary metastases; some were classed as endothelioma.

NEUROBLASTOMA OF ADRENAL ORIGIN

Neuroblastoma of adrenal origin is a highly lethal disease of early life which may be associated with secondary deposits in bone. This tumor arises from the parent cell in the adrenal medulla, the neuroblast, or occasionally in some other portion of the sympathetic nervous system. Two varieties are recognized; the Pepper form and the Hutchinson form. The former, arising in children usually under 2 years of age, runs a rapidly fatal course with liver and retroperitoneal tissue chiefly affected. The Hutchinson form, which presents marked skeletal manifestations, is seen more frequently between the ages of 2 and 7. Cranial deposits produce exophthalmus,

gradual skull expansion, and diastasis of the sutures. The lesions in the long bones are destructive rather than productive and occupy diversified locations (see Fig. 234).



FIG. 231. Metastasis from teratoma testis in a 15-year-old boy. Note close resemblance to primary bone sarcoma occurring at an age when the latter is most often seen.



FIG. 232. Metastatic carcinoma of ulna from primary cancer of the lung.

This disease constitutes a rather frequent diagnostic problem in the Children's Ward of Memorial Hospital because it is so difficult to distinguish it from Ewing's sarcoma when the bone lesions predominate. The similarity is not confined to the roentgenographic appearance but includes the histologic as well. Not infrequently a report is received that the lesion is either Ewing's sarcoma or metastatic neuroblastoma. We can recall instances where this difficulty persisted even after a complete postmortem examination. Fortunately it has been our experience that these metastatic neuroblastomas are radiosensitive. Also we have recently observed instances in which tumors have decreased markedly in size following a course of

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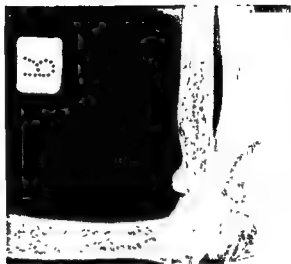


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Coley's toxins. It is, therefore, our present opinion that when such a condition is suspected the child ought to be treated with both agents. Roentgen therapy in moderately heavy doses has caused complete disappearance



FIG. 233. Metastatic bronchogenic carcinoma of the humerus.



FIG. 234. Metastatic neuroblastoma of humerus.

of sizable metastatic tumors. The ultimate prognosis, however, is exceedingly unfavorable.

37. HODGKIN'S DISEASE AND LYMPHOSARCOMA

THE IMPORTANCE OF THESE TWO LYMPHOMATOID DISEASES AS A CAUSE OF skeletal involvement lies in the fact that occasional cases are found in which the principal lesions are osseous, and lymphadenopathy is not striking so that the diagnosis between them and metastatic carcinoma or even primary bone sarcoma is rendered difficult (see Fig. 235).

We shall pass over the fact that in terminal cases of Hodgkin's disease marrow involvement is almost constant. Nor are we particularly concerned with the high incidence of such involvement (49 per cent in Hodgkin's disease and 29 per cent in lymphosarcoma) found at autopsy by Vieta, Friedell, and Craver (see Fig. 236). Actual cortical destruction visible on the roentgenogram was found by these authors to be present in 14.8 per cent of 257 cases of Hodgkin's disease and in 7 per cent of 213 cases of lymphosarcoma. The actual incidence is undoubtedly much higher because only a small proportion of the cases had adequate skeletal roentgenographic study, which in cases of absent or few symptoms is often omitted.

Lesions originating in the bone marrow can be recognized roentgenographically only when the disease has extensively affected the spongiosa or advanced to cortical destruction. Far-advanced lesions found at autopsy may have escaped detection on roentgenograms. Films made to demonstrate bone detail with the utmost clarity would unquestionably eliminate some of these negative findings.

Cortical destruction is more rapid and extensive in lymphosarcoma and the incidence is more accurately shown by roentgenography than in Hodgkin's disease where foci may exist for a longer period in bone before actual destruction takes place.

Among the unusual sources of bone metastasis is transitional cell epithelioma of the nasopharynx. A striking example of metastasis from this source is shown in Figure 237.

SYMPTOMS

Pain and tenderness are the earliest and most persistent complaints in both Hodgkin's disease and lymphosarcoma. Tenderness on pressure is a reliable sign and this symptom usually indicates the presence of underlying bone destruction. While a mass is not often felt in the long bones it can frequently be detected in the ribs or sternum. Such masses are usually tender.



FIG. 235. Osseous metastasis from Hodgkin's disease.

Metastasis to bone occurs by lymphatic extension directly from the affected lymph node or by the blood stream to bones at a distance. Uehlinger has discussed these modes of dissemination; he found that of 17 cases, 12 were due to direct extension and 5 by hematogenous spread. His figures were arrived at after postmortem examination. Craver, however, from his analysis of Memorial Hospital cases, believes that the blood stream is the more frequent mode of dissemination in Hodgkin's disease and that this is even more true in lymphosarcoma. Regions in which red marrow predominates are more often affected, the distribution paralleling that found in metastatic carcinoma of bone. According to Craver, no authentic case of supposed primary Hodgkin's disease of bone has been reported without concomitant disease in lymph nodes, liver, or spleen. Reticulum cell sar-

coma of lymph nodes and associated bone lesions is not uncommon and must be carefully distinguished from the primary reticulum cell sarcoma of bone first described by Parker and Jackson (see Fig. 331, p. 612). We have excluded from this category all cases where bone involvement was not the primary manifestation of the disease. Distribution of the skeletal lesions in 38 cases of Hodgkin's disease and 15 cases of lymphosarcoma is shown in Figure 238.

CHARACTER OF THE BONE LESION

In the Memorial Hospital series already referred to, which included 38 cases of Hodgkin's disease, there were 144 bones showing roent-



FIG. 236

FIG. 236. Hodgkin's disease of right second rib. In this case the first symptom was referable to the rib lesion and a tentative roentgenographic diagnosis of Ewing's sarcoma or inflammatory bone disease was rendered. The presence of an enlarged hilar node was the only suggestive finding pointing to Hodgkin's disease. Diagnosis was finally confirmed at autopsy.



FIG. 237

FIG. 237. Metastatic transitional cell epithelioma (pharynx). (Courtesy of Parkland Hospital, Dallas, Texas.)

genographic evidence of disease; the lesions were either osteoblastic, osteolytic, or a combination of both. The latter, or mixed type, predominated (58 per cent), the purely osteolytic was found in 28 per cent, and the solely osteoblastic variety in 14 per cent. Various types of lesions were observed in the same individual. Periosteal reactive bone formation was seen only in moderate degree, never as the sole bone change, and primarily in the pipe bones, the sternum and ribs. Fractures of ribs and vertebrae were observed but complete collapse of a vertebral body, such as may be seen in metastatic carcinoma, was not encountered in a single instance.

In lymphosarcoma, on the other hand, the nature of the bone lesions was quite different. In 85 per cent of the series under consideration the areas were osteolytic, in 10 per cent mixed, and only 5 per cent were osteoblastic.

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In the Memorial Hospital series already referred to, which included 8 cases of Hodgkin's disease, there were 144 bones showing roent-



FIG. 236

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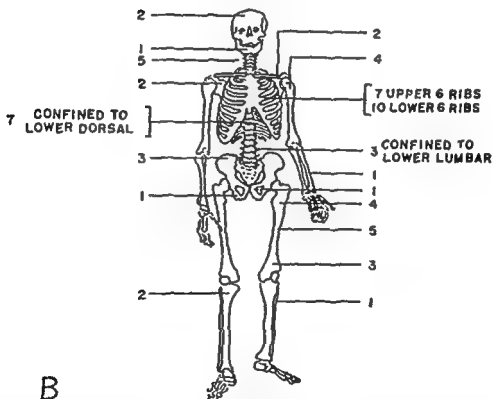
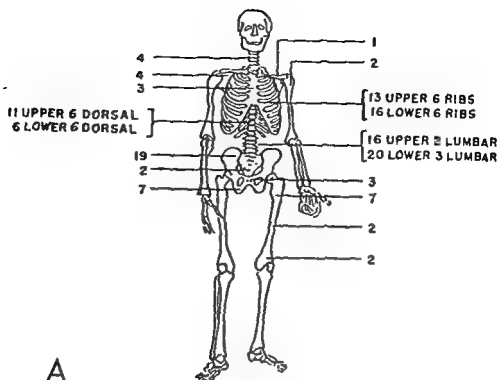


FIG. 238. A, Distribution of skeletal lesions in fifteen cases of lymphosarcoma. B, Distribution of skeletal lesions in thirty-eight cases of Hodgkin's disease. (Craver, L. F., and Copeland, M. D. Changes in the bone in Hodgkin's granuloma. *Arch. Surg.* 28:1062, 1934.)

In most cases the osteolytic lesions are more extensive and more invasive than in Hodgkin's disease and often advance to nearly complete dissolution of the affected area. Compression of the vertebral bodies is more complete. Periosteal reaction is more marked but again it occurs only in the long bones.

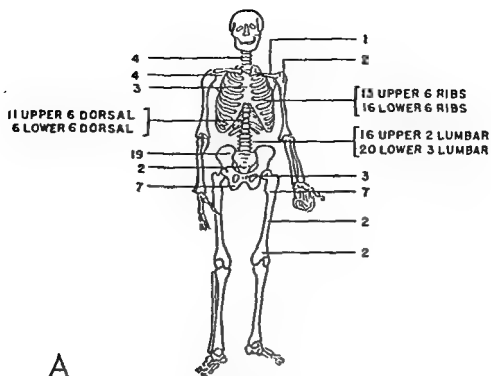
TREATMENT

The logical method of treatment is irradiation. Pain is usually relieved promptly even where bone changes are extensive. Restoration of bone by repair after roentgen therapy is not constant but in a third of the cases it may be completely or nearly so. Lesions in flat bones seem to show the best response and the osteolytic areas are more favorably influenced than are the mixed or purely osteoblastic types.

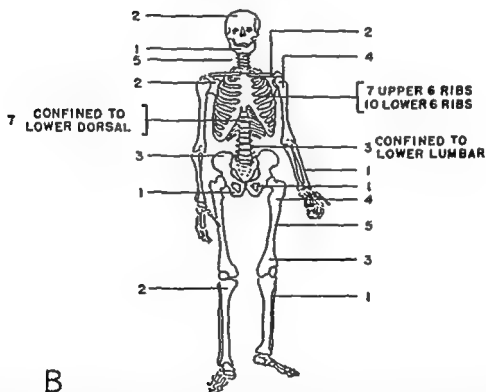
A satisfactory dose is from 1500 to 2000 r measured in air, given with 200 kv. and by fractional doses distributed over several months. Estimation of tissue dosage is generally impractical.

One should aim at alleviation of symptoms rather than restoration of bone. In cases where vertebral involvement is associated with neurologic signs improvement or complete relief may be anticipated.

Pain is also ameliorated in lymphosarcoma, but since skeletal invasion is usually a terminal phenomenon the results are less dramatic.



A



B

FIG. 238. A, Distribution of skeletal lesions in fifteen cases of lymphosarcoma. B, Distribution of skeletal lesions in thirty-eight cases of Hodgkin's disease. (Craver, L. F., and Copeland, M. D. Changes in the bone in Hodgkin's granuloma. *Arch Surg.* 28:1062, 1934.)

In most cases the osteolytic lesions are more extensive and more invasive than in Hodgkin's disease and often advance to nearly complete dissolution of the affected area. Compression of the vertebral bodies is more complete. Periosteal reaction is more marked but again it occurs only in the long bones.

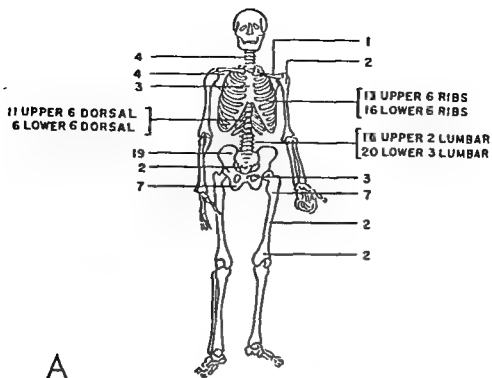
TREATMENT

The logical method of treatment is irradiation. Pain is usually relieved promptly even where bone changes are extensive. Restoration of bone by repair after roentgen therapy is not constant but in a third of the cases it may be completely or nearly so. Lesions in flat bones seem to show the best response and the osteolytic areas are more favorably influenced than are the mixed or purely osteoblastic types.

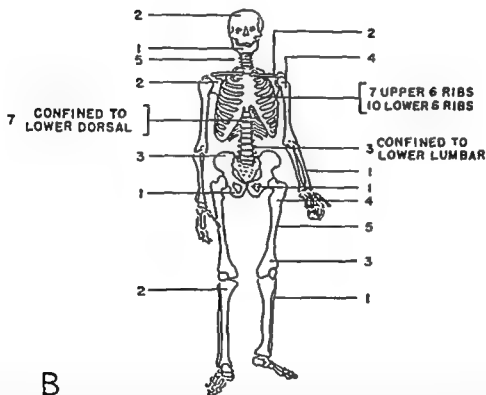
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38. METASTATIC SARCOMA

SECONDARY SKELETAL INVOLVEMENT FROM PRIMARY TUMORS OF BONE, with the notable exception of Ewing's sarcoma, is rare. We have observed less than a half-dozen instances of osteogenic sarcoma in which this has occurred. In several cases the question has been raised as to whether these were separate, independent, primary tumors or whether some of them were metastatic. One cannot easily decide this matter; each case must be considered in the light of the time interval and the presence of pulmonary metastases at the time the second bone tumor is recognized.

Endothelioma (Ewing's sarcoma), however, has a predilection for skeletal metastases. It is rare to see a case that progresses to the usual fatal termination without the appearance of multiple metastatic foci in such bones as the skull, pelvis, and long bones (see Fig. 175, p. 303).

Lymphosarcoma occasionally spreads by the blood stream to bone where it sets up an osteolytic secondary growth.

Neurogenic sarcoma seldom gives rise to skeletal metastases; where the growth lies in proximity to a bone, however, it may invade it by direct extension.

TREATMENT

Palliative treatment is all that can be offered in metastatic bone sarcoma, whether it be the lungs or other bones that are affected. This is true also of skeletal metastases from soft-tissue sarcomas of lymphomatous, neurogenic, or lipogenic origin, and those of Hodgkin's disease. Therefore the decision to treat bone lesions with radiation should rest upon the radiosensitivity of the primary tumor. Ewing's sarcoma, reticulum cell sarcoma, metastatic lymphosarcoma, and, to a less marked degree, anaplastic liposarcoma, are radiosensitive and the secondary areas show regression comparable to that obtained in the primary growth. Neurogenic sarcoma, on the other hand, is radioresistant and no more useful purpose is attained by employing roentgen therapy to areas of secondary involvement than is accomplished by irradiating the original tumor; in both instances little or nothing is gained.

The mistake is frequently made of giving heavy exposures of roentgen rays to large areas of the body in an attempt to irradiate all demonstrable skeletal deposits even though the patient's symptoms may be referable to but one or two foci. These alone should be treated and further therapy reserved for other areas, when and if they give rise to symptoms.

39. LEUKEMIA

LEUKEMIA IS NOT A COMMON CAUSE OF GROSS BONE LESIONS. CRAVER AND Copeland found only 6 instances roentgenographically in a series of 86 patients with lymphoid leukemia and only 1 instance in 82 patients with myeloid leukemia.



FIG. 239. Extensive involvement of vertebral column in leukemia. Microscopic confirmation.

It has been shown that bones which normally contain red marrow—such as the ribs, spine, and skull—have a higher incidence (see Fig. 239).

Craver and Copeland's cases, in the order of frequency, affected femur, humerus, pelvis, skull, metacarpals, ulna, and vertebrae. Both osteoblastic

and osteolytic changes occurred. Periosteal reaction was infrequent. Osteoporotic changes were most often found. These authors also observed that gross involvement of bone occurred more often in low-grade lymphatic leukemia than in cases that had high white cell counts.

In the differential diagnosis one must consider primary reticulum cell sarcoma of bone, myeloma, metastatic carcinoma, Hodgkin's disease, lymphosarcoma, and osteomyelitis.

Treatment with high-voltage roentgen rays in moderate doses may relieve pain and result in bone repair. The general course of the disease is unaltered by the presence of skeletal involvement.

40. GENERAL CONSIDERATIONS

SYMPTOMS

PATIENTS WITH METASTATIC TUMORS OF BONE MAY REMAIN SINGULARLY free from symptoms but as a rule pain is the most constant and most troublesome complaint. It varies markedly in its severity, being manifest earlier in weight-bearing portions of the skeleton or where there is muscular pull or stress on the bone. Often the pain is considered "rheumatic" because it is not severe nor constant in the earlier stages. Many of these patients, therefore, are treated extensively with local massage, heat, and other forms of physical therapy. The early roentgenographic examination is negative. Very often by the time the patient consults a physician because of pain, there is roentgenographic evidence of bone alteration detectable by a competent roentgenologist. In the face of continuing symptoms, further examination at a later date will disclose the condition which may not have been evident on the initial films.

PHYSICAL SIGNS

In most cases of skeletal metastasis early positive physical signs are notably absent. However, certain types of carcinoma may produce bulky swelling, e.g., thyroid, but much depends upon the bone involved and its situation as regards surface anatomy. Ordinarily, swelling is a late occurrence and even with widespread dissemination there may be no palpable or visible tumefaction; thus our dependence is chiefly upon the roentgenographic findings. Too great importance cannot be placed upon the need for early films when pain is complained of by a patient known to have had a carcinoma.

Pathologic fracture may be the first finding to suggest the presence of bone metastasis. It may follow a trivial injury or occur without any apparent trauma. Usually the films taken after the fracture has occurred will reveal underlying bone destruction. In the occasional case, however, particularly if the accompanying injury is of moderate or severe degree, the fact that there is underlying bone pathology may be overlooked and a diagnosis of simple fracture made; in such instances subsequent films will demonstrate the true nature of the lesion and a restudy of the earlier films will usually reveal its presence.

In advanced cases, pain may become intolerable and require increasingly larger doses of opiates. Vertebral destruction may be wholly unsuspected until collapse occurs with sudden partial paralysis.

Anemia of secondary type, weight loss, and cachexia are by no means constant even in the presence of multiple areas of bone metastases. On the other hand, absence of these findings should not disarm suspicion.

PATHOLOGIC FRACTURE

One of the distressing features of metastatic disease of bone is the occurrence of pathologic fracture. This may vary in degree from a slight cortical crack to a complete fracture with bulky tumor formation. Displacement is usually not marked. Although untreated fractures occasionally heal spontaneously, the union is not long sustained and refracture is the rule. Radiation is of value in bringing about regression of the tumor and repair of the fracture, providing the lesion is radiosensitive and the dosage employed is not so heavy as to inhibit the natural processes of bone repair (see Chap. 56).

While this method of treatment shows some degree of promise in affording palliation in a number of patients, it still must be used cautiously and a careful roentgen survey and blood-chemistry assay should accompany the clinical therapy.

LABORATORY FINDINGS

Clinical laboratory procedures are contributory chiefly for the purpose of excluding other conditions which give rise to similar bone changes. Serum phosphorus, calcium, phosphatase, serum protein, serologic test for syphilis, and test for Bence-Jones bodies in the urine are all of value.

For a detailed consideration of the interpretation of blood chemistry in bone tumors see Chapter 5.

ROENTGENOGRAPHIC APPEARANCE

In suspected areas much information may be afforded by roentgen-ray examination which should include the entire skeleton. Where no obvious primary lesion can be found, intravenous urography and chest films are indicated; the former may point to the kidney while the latter may disclose a bronchogenic tumor. Prostatic examination may suggest a carcinoma of that organ and careful palpation of the thyroid or breast may reveal small and easily overlooked tumors which are the primary source. In every suspicious bone lesion discovered in a person over 30 years of age a most thorough physical examination is mandatory. It will often disclose a primary source which otherwise might have been overlooked.

DIFFERENTIAL DIAGNOSIS

If after a thorough investigation including laboratory, roentgenographic, and clinical study, the diagnosis of the suspected bone lesion cannot be established, a biopsy is justified. While in some cases no primary cancer can be discovered during the patient's life, and even autopsy may fail to establish the source of the metastasis, a pathologist can usually determine from a biopsy whether the lesion is primary or metastatic. This is of importance where the area is a solitary one, for should it prove to be a primary bone tumor prompt radical surgery might be indicated, whereas in the presence of metastatic bone disease such procedure is seldom justified. Osteolytic metastasis, when single, must also be distinguished from eosinophilic granuloma, solitary plasma cell myeloma, primary liposarcoma, and certain osteolytic central sarcomas.

Age is of assistance in making a diagnosis since metastatic cancer is rarely found in persons under 30 and primary bone sarcoma is uncommon after that age.

We have found aspiration biopsy to be of great value, particularly in suspected bone metastasis; e.g., a tumor of the sacroiliac region was found on aspiration to be metastatic, and thereafter a small nodule about 1 cm. in diameter was discovered deep in a voluminous breast, which had escaped notice in a complete physical examination in the Admitting Department. Removal of the breast tumor revealed a structure which the pathologist found to be identical with that of the aspirated sacroiliac metastasis. We have used aspiration biopsy successfully in lesions of the cervical and lumbar spine where a formal surgical biopsy is not a trivial procedure (see Chap. 3).

TREATMENT

ROENTGEN THERAPY

In view of the ultimate prognosis which is uniformly bad, treatment of bone metastases should be directed toward the relief of symptoms for as long a period as possible and the prevention of a pathologic fracture; the former is accomplished remarkably in some cases, only moderately in others, and scarcely at all in the rest. Response to irradiation is what determines the palliation, and this in turn depends upon the individual tumor's radiosensitivity. Frequently the pathologist can estimate the likelihood of an individual tumor proving radiosensitive, yet we have seen a most extraordinary response on the part of some tumors whose microscopic appearance denied even moderate radiosensitivity. For this reason and partly because no other methods of specific therapy are at present available, it is justifiable to give roentgen therapy a trial in every case unless biochemical treatment is applicable. If it produces relief of pain in

the region irradiated, other areas of involvement, especially those causing pain, should also receive treatment. If response is lacking, it is unwise to continue with roentgen therapy indefinitely. However, in about 25 per cent of the cases, relief of pain and objective improvement in the appearance of the films of the bone areas are obtained, and such cases seem to enjoy a definite prolongation of life as a result of the treatment.

The dosage is a matter for careful consideration. The optimum desired is that amount which will produce a maximal regression of the tumor with but a minimal interference with bone regeneration. Doses large enough to destroy cancer cells are not to be recommended for they may do the patient more harm than good. Excessive doses will only render a pathologic fracture more imminent. It should never be lost sight of that a cure is not the aim and that palliation is not always in proportion to the total dosage of roentgen rays employed. One must guard especially against treatments to many areas of the trunk where vital soft parts and the hemopoietic system are exposed. Radiation may add to the patient's distress rather than alleviate it. Its judicious administration in these cases is an art which can be cultivated and which wide experience enhances.

BIOCHEMICAL THERAPY

The effect of hormones on certain tumors, such as prostatic cancer in males and mammary cancer in females, has long been observed and much experimental study in this field has been carried out. The profound effect of castration on mammary and prostatic carcinoma is well known. We have repeatedly observed instances where castration by roentgen rays has affected mammary carcinomatous areas in bone and in some a prolonged period of relief has been obtained. Huggins' work on prostatic cancer by means of orchiectomy is noteworthy. Whether hormone therapy can produce permanent cures, however, is doubtful. This in no way detracts from its importance as a useful additional method of affording palliation which is in some cases dramatic and long sustained, and it may prove to be a good alternative treatment to roentgen therapy, especially in younger patients.

A small number of men with primary or recurrent inoperable mammary cancer secondarily invading bone or soft parts have been castrated. The results of this procedure have been reported. Why orchiectomy in male patients with the disease localized in bone should be a fairly successful clinical procedure in the majority of instances requires further study for a satisfactory explanation. However, these patients with no other therapy than orchiectomy show healing in the metastatic foci and a diminution in blood calcium and alkaline phosphatase.

Fels believes that the favorable results obtained with testosterone propionate in his 3 cases of mammary cancer demonstrates that further extensive trial is warranted.

The therapy of metastatic mammary cancer, especially when it involves bone, has been the subject of clinical and laboratory investigations at Memorial Hospital. The latter investigation has been concerned with the blood changes which followed the administration of sex hormones. It was found by Farrow and Woodard that the administration of the male sex hormone to a patient with metastatic mammary cancer was so deleterious that all the bone lesions were greatly activated and a severe hypercalcemia ensued. In fact, the amount of calcium circulating in the blood was so excessive that marked nausea and vomiting were produced.

Farrow and Woodard's original work on the administration of testosterone propionate is now receiving a very thorough test. It is probably premature at this time to attempt any definite conclusion on the value of this therapeutic procedure but many of these patients with bone metastases from breast carcinoma experience a varied measure of relief from pain. In addition, they show some increased calcification in the osseous lesions for variable periods of time.

The majority of patients with metastatic lesions in the soft parts, especially the lung, exhibit very little change, but they may infrequently show improvement.

SURGICAL TREATMENT

While little attempt has been made by surgeons to resect solitary metastatic sarcomas or carcinomas of the lungs, since the outlook from any other method of treatment is invariably hopeless it would seem worth while at least to make the attempt. It is the opinion of some that this method will be used more widely in the future.

The most recent comprehensive communication on the subject of pulmonary resection for metastatic neoplasms is that of Alexander and Haight who report upon 24 collected cases from various clinics. Of these, 12 are apparently free from recurrence, 4 with less than one year follow-up and 8 traced for a longer period (12, 7, 6, 5, 4, 3, 1½, and 1 year).

These authors list the important criteria for operative removal of a solitary metastatic lesion in the lung as follows:

1. A thorough physical and roentgenographic examination shall have discovered no other metastasis. Such an examination should include careful palpation for enlargement of lymph nodes and liver and for tumors in the skin, bones, and all palpable organs. The chest roentgenographic examination should include stereoscopic posteroanterior projection films and lateral or oblique projections, as well as fluoroscopy in all standard projections. X-ray films of the skull and all the long bones may be worth making.

2. Reasonable assurance should be had that the primary neoplasm has been completely removed. This is given if the primary neoplasm was removed 3 or more years before the contemplated pulmonary operation without the signs or

symptoms of recurrence. In doubtful cases, an exploratory operation and removal of a biopsy specimen may be advisable.

3. The patient must be in sufficiently good general condition for the contemplated pulmonary operation and, with regard to pulmonary function, able to spare a lung, a lobe, or a part of a lobe, the extent of the resection depending upon the extent and location of the neoplasm.

The length of time that has passed between the complete removal of the primary neoplasm and the appearance of the presumed solitary metastatic lesion in a lung is important with regard to the validity of an assumption that the single demonstrable metastasis is actually the only one. If only one metastatic lesion (especially if it is a large one) can be found several years after the primary lesion has been removed, there is probably a better chance that no other metastases exist than if the metastatic lesion were found shortly before or after removal of the primary lesion because, in the latter instance, relatively little time has passed for the development of other metastases. This argument, however, is not wholly sound and not always applicable since the late appearance of a single small metastasis strongly suggests that it has been dormant or of a low grade malignancy and, therefore, that if other metastases are present they, too, may be small and not yet clinically demonstrable because of the absence of symptoms and physical and roentgenographic signs. The lung, owing to its radiotranslucency, is a particularly favorable organ for the very early detection of a metastasis, perhaps before metastases in other organs can be found. It should be noted, however, that the discovery of a single pulmonary metastasis soon after, or even before, the removal of the primary neoplasm does not necessarily indicate that other metastases will appear later. With due allowance for the exceptions mentioned, however, the late appearance of a single metastasis offers a better chance that other metastases are not present than if the single metastasis appeared early.

It is significant that 6 of the 8 sarcomas included in the 24 cases were apparently free of recurrence, whereas, only 6 of the 15 carcinomas that survived operation were apparently free of disease. It thus appears that there is a greater justification for pulmonary resection in cases of sarcoma.

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SECTION SIX

Tumors of Bone in Special Localities

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INTRODUCTION TO SECTION SIX

ALTHOUGH THE USUAL SITE OF ORIGIN OF PRIMARY BONE TUMORS (excluding myeloma) is in the long pipe bones, there are certain other localities which deserve special mention since sarcomas arising therein are more difficult to diagnose and to treat. The diagnosis is more uncertain because the roentgenographic criteria are less clearly defined. The treatment is rendered more difficult by the inaccessibility of the tumor or because it cannot be removed as widely as in the case of a lesion of the extremities where amputation is usually possible. In some of these cases it may be necessary to rely on roentgen therapy alone.

Before taking up these tumors separately there are certain observations to be made.

Those tumors which may be resected widely include the following: sarcoma and adamantinoma of jaw, benign and borderline tumors of the rib and of the lower portion of the sternum, and selected cases of chondroma or low-grade chondrosarcoma of the ilium, ischium, and pubic bones where the extent of the involvement does not demand hemipelvectomy.

Malignant tumors of the bones of the hands and feet are notable for their rarity. Sarcoma of the carpal and tarsal bones is rare. The same is true of the metacarpals and metatarsals; occasional instances of metastatic cancer affecting these bones have been reported. Primary bone sarcoma of a phalanx is so rare as to be considered almost nonexistent.

These facts being accepted, conservative measures find their greatest applicability to tumors of the bones of the hands and feet. Curettage and chemical cauterization of central chondromas of the phalanges and the metacarpals yield satisfactory results. Amputation should seldom be required for bone tumors of the fingers, and practically never considered for the entire hand. Here, partial amputation should take precedence; conservatism is justified by the rarity of invasive malignant bone tumors.

Tumors of the axial skeleton are especially difficult to treat. Some cases of sarcoma, hemangioma, or meningioma of the skull may be treated by wide resection with or without tantalum replacement. Unless the neoplasm is confined to a process rather than to the body of a vertebra, surgical extir-

pation is not practical. Hemangioma and giant cell tumor involving the spine may yield good results following the administration of moderate doses of roentgen therapy.

Tumors of the pelvic bones have usually been considered unsuitable for surgery, and in the past reliance has been placed upon roentgen therapy. Hemipelvectomy is now being used more often for selected cases of iliac, pubic, and ischial neoplasms. Aside from the giant cell tumor, the chondrosarcoma, and the osteogenic sarcoma, the sacrum may be the site of a sacral chordoma which still constitutes a challenge to our surgical attack.

Metastatic cancer finds its way with great frequency into the skull, spine, ribs, and all the pelvic bones. While usually multiple, these lesions on the first examination may appear to be solitary. In such instances a primary tumor may be suspected. Plasma cell myeloma is similar in its distribution to sites of red marrow; it too sometimes appears to be monostotic.

From the foregoing remarks, it becomes apparent that there is a need for the early establishment of the diagnosis in tumors of these special localities just as there is for tumors of the major long bones of the extremities.

4I. TUMORS OF THE SKULL

THE CRANIAL BONES MAY BE THE SITE OF BENIGN TUMORS, PRIMARY malignant bone tumors, metastases from cancer arising in other organs, and from Ewing's sarcoma primary in other bones. Benign tumors are un-



FIG. 240. Ivory-like osteoma of skull involving frontal sinus. (Hunterian specimen, Royal College of Surgeons.)

common, primary bone sarcomas are rare, while metastatic cancer and secondary involvement from Ewing's sarcoma are encountered rather frequently.

OSTEOMA

Osteoma is the most common benign tumor of the skull. It is notable for its slow rate of growth, and its tendency to present a well-circumscribed mound-like swelling which is extremely hard, fixed, and usually quite painless (see Fig. 240). It is generally noted in childhood or early adult life; it may have been present for two or more decades when first seen in a tumor clinic. Many of the patients will ascribe the onset of the swelling to a pre-

vious trauma, such as a fall or a severe blow. The frontal bone is the one most often affected, the parietal and temporal bones much less frequently, and the occipital bone very rarely.

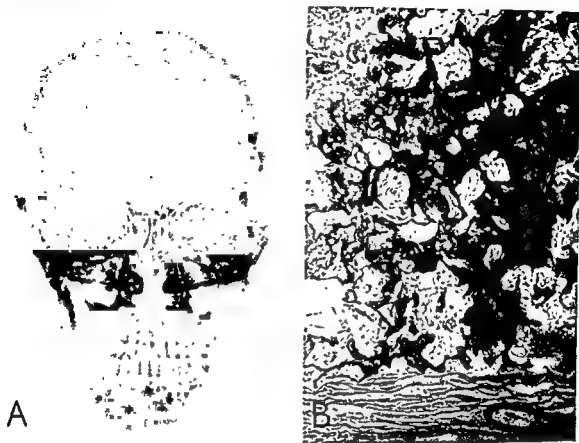


FIG. 241. A, Osteochondroma of sella turcica. B, Microphotograph shows chondromatous tissue. (William Beaumont General Hospital.)

The roentgenographic appearance is characteristic. It is that of a well-circumscribed area of dense new bone which has a sharp line of demarcation at its base formed by the inner table and a smooth external surface which is convex.

OSTEOCHONDROMA

Intracranial osteochondromas are rare. They may be of extremely slow growth and yet cause the death of the patient. An example is shown in Figure 241 which represents a case seen in William Beaumont General Hospital, in which the tumor arose from the sella turcica and eroded a branch of the circle of Willis to cause death from intracranial hemorrhage. This case was reported by King and Butcher.

ANGIOMA

One of the sites in which angioma of bone is most often seen is the skull. It may remain apparently stationary for long periods and give rise to no

important symptoms other than a slight irregularity in the contour of the outer table. The parietal and frontal bones are favorite sites (see Fig. 242). The appearance seen on roentgenograms is often diagnostic. There is a



FIG. 242. Hemangioma of skull.

fine mottled osteoporosis resembling foam rubber and projecting striations of spicules of bone radiating from the tumor. The process is sharply delimited.



FIG. 243. Monostotic fibrous dysplasia of skull.

GIANT CELL TUMOR

This variety of bone neoplasm is exceedingly rare in bones of the calvarium. We believe it probable that such cases as have been described may have been examples of fibrous dysplasia with giant cells present in the periphery of the lesion.

FIBROUS DYSPLASIA

The skull may be the seat of extensive changes produced by areas of fibrous dysplasia and such areas may be monostotic or part of a polyostotic



FIG. 244. Fibrous dysplasia of skull. Left frontal and right malar bone regions are prominently affected. Patient presented other bone lesions and pigmentation but gave no definite history of sexual precocity.

form of the disease. In a series of 67 cases of fibrous dysplasia in isolated bones (monostotic) Schlumberger found 5 in the calvarium; 2 in the frontal bone and 1 each in the temporal, parietal, and occipital bones (see Figs. 243-245).

OSTEOGENIC SARCOMA

The calvarium is only rarely the seat of primary osteogenic sarcoma. At Memorial Hospital there have been only 7 cases in a period of twenty years. Geschickter and Copeland state that in a series of over 500 cases of primary bone sarcoma there were only 8 examples of osteogenic sarcoma of the cranial bones. As in this disease in general, children and young adults are principally affected, with the exception of that form of osteogenic sarcoma which is associated with Paget's disease, and which occurs in individuals past middle life.

The types of osteogenic sarcoma seen elsewhere are represented in this location, e.g., osteolytic, sclerosing, chondrosarcoma, etc. The tables of the skull are invaded and destroyed and soft-part swelling is produced by extension to the overlying tissues. The symptoms most often noted are swelling and headache. The roentgenographic appearance may enable one to make the correct diagnosis in most instances but aspiration or formal biopsy is needed for confirmation.

Chondrosarcoma is more often seen in the base of the skull and may develop in a pre-existing chondroma, although it can occur in the occiput (see Fig. 246). Treatment either by irradiation or



FIG. 245. Advanced skull changes in fibrous dysplasia

attempts at surgical extirpation have been singularly unsuccessful, and in untreated cases the tumor tends to increase steadily in size and to metastasize.

In the 7 cases referred to above the parietal bone was the primary site in 3, the zygoma in 2, and the malar and ethmoid bone in 1 each.

Surgical removal, preoperative and postoperative irradiation, and irradiation alone were the methods employed in this small series. In none was a five-year survival obtained.

EWING'S SARCOMA

This type is only rarely primary in the skull. In the Memorial Hospital series of 136 cases only 3 were found in this area. Since this disease tends to metastasize to the skull from a primary site elsewhere it may be difficult to determine in those cases where skull and other bones are involved whether the cranial lesion is metastatic or primary.



FIG. 246. Osteogenic sarcoma of occipital region arising in a patient who had sustained a direct trauma to this area.

The tumor is predominantly osteolytic but produces bulky, often huge soft-part swellings (see Fig. 175, p. 303). The treatment of patients with this condition affecting the skull has been uniformly unsuccessful although the temporary palliative effect of irradiation has sometimes been decidedly worthwhile.

CRANIAL CHORDOMA

The tendency of chordoma to occur at the ends of the axial skeleton is well known. Sacral chordoma will be discussed in the Chapter dealing with "Tumors of the Pelvic Bones."

Those chordomas which arise at the opposite end of the spinal axis occur most often at the clivus blumenbachii or at the spheno-occipital synchondrosis, and require mention among tumors of the skull. They share the same tendency to destroy bone and to affect the adjacent tissues both within and without the cranium, as does the sacral form in the pelvis. For further comment on the characteristics of chordoma see pages 452-457. Metastasis from chordoma is decidedly rare.

CASE REPORT

G.Z., male, aged 18 years, was admitted to Memorial Hospital on March 27, 1934, with a history of swelling of the left temporal region over a period of approximately two months. About three months prior to his admission, while

playing basketball, he had been struck on the left temple by the elbow of another player. About a month later he had noticed a swelling of this region at the exact site of the injury, which had progressively increased in size. For two or three weeks he had complained of left-sided headache which was more troublesome at night. There were no other cerebral symptoms. His appetite was fair, his digestion good, but there was a weight-loss of 16 pounds since the onset of symptoms.

Physical examination revealed a well-developed and well-nourished youth in good condition, whose only significant abnormal findings were referable to the head. There was a large, moundlike, rounded swelling of bony hardness, firmly attached to the skull, which centered in the left temporal region and extended anteriorly to the outer corner of the mandible, posteriorly to the mastoid process, and superiorly to the temporo-parietal articulation (see Fig. 247). The left temporo-mandibular joint was apparently pushed forward by the tumor since there was a protrusion of the mandible which was not present before the onset of symptoms. The left ear was pushed outward and downward and the auditory canal was somewhat compressed from above. The mass was of homogenous bony hardness. There was an incisional scar over the most prominent portion (biopsy). The tumor measured roughly 12 x 12 cm. and was elevated about 4 cm. above the surface of the skull.




FIG. 247. Roentgenographic appearance of osteogenic sarcoma originating in the temporal region following a single acute trauma. This tumor appears to have arisen in an ossifying hematoma rather than primarily in the bone of the skull itself. Microscopic diagnosis: osteogenic sarcoma. Patient died of the disease.

Roentgenographic examination of the skull on Mar. 27, 1934, was reported by Dr. Herendeen as follows: "Films show evidence of a partly calcified mass protruding from the left temporal region corresponding to the clinically observed tumor. This finding is consistent with the clinical diagnosis of osteogenic sarcoma of the skull. Film of the chest shows no evidence of pulmonary metastases."

A number of the members of the Staff of Memorial Hospital examined this patient and expressed divergent views as to the diagnosis. Dr. Ewing, after studying sections from the biopsy performed in Ohio (Department of Pathology, Ohio State University), reported as follows: "I cannot make a diagnosis of sarcoma from this material yet see no reason for the failure of diagnosis of sarcoma were it present since the material is adequate. It has the general appearance of myositis ossificans. There is much old hyalinized tissue which on cross section looks like necrotic muscle. The calcification is not tumor bone but calcification

in an inflammatory process. There are areas of cartilage which resemble fully developed adult cartilage. We know that cartilage occurs in myositis. It is not the type seen in osteogenic chondrosarcoma. I think any aggressive treatment should be withheld until further diagnosis is made."

Because of the difference of opinion held concerning the diagnosis, Dr. William B. Coley performed a second biopsy on April 4, 1934, reporting as follows:

"Finding: Over the left temple region is a swelling, measuring approximately 10 cm. in diameter, and approximately 1 or 2 cm. in thickness. The mass seems to be localized to the muscle, in which there was a grayish-white, friable material, which appeared somewhat like necrotic or tumor muscle. It did not seem to invade the skull."

From the material thus obtained Dr. Stewart made an unequivocal diagnosis of osteogenic sarcoma. (Incidentally, this was supported by an examination of autopsy material some months later which showed metastases to muscle and kidney.)

Following the second biopsy the temporal region was treated with 70,000 mg. hours given by radium-element pack in doses of about 8000 mg. hours per treatment over the period from Mar. 28 to Apr. 17, 1934. In addition, three doses of Coley's toxins were injected intramuscularly. The patient was discharged from the hospital on Apr. 17 and died of general metastases on Aug. 30, 1934.

While this case is recorded as an example of osteogenic sarcoma of the skull, it seems more probable that it was an instance of extraskeletal osteogenic sarcoma arising from an area of myositis ossificans in the temporal muscle and was indirectly due to the injury sustained in the area of temporal muscle where the tumor subsequently arose.

METASTATIC SKULL TUMORS

Theoretically any malignant tumor may spread to the bones of the skull but metastases are seen in this location comparatively infrequently except when the primary tumor is of mammary or prostatic origin, and even then only involve the skull when there is widespread dissemination. Multiple areas of bone destruction in the calvarium are more often due to metastases than to cancer metastases but their discovery should be followed by complete skeletal roentgenography and a search for the existence of a primary growth. Paget's disease may give rise to changes in the bones of the skull which may be difficult to distinguish from osteoblastic prostatic metastases. The former is associated with an elevation of the alkaline serum phosphatase while the acid phosphatase is elevated in prostatic cancer metastases.

NONNEOPLASTIC SKULL LESIONS

HAND-SCHÜLLER-CHRISTIAN'S DISEASE

Circumscribed areas of destruction of the bones of the skull are seen in children with Hand-Schüller-Christian's syndrome. The disease is characterized by the presence of multiple areas of bone destruction in the skull, often associated with exophthalmos and diabetes insipidus.

these areas has given rise to the term *maplike skull*. Such lesions often yield dramatic results to mild doses of roentgen-rays.

PAGET'S DISEASE

The skull is one of the most consistently affected sites of Paget's disease. It is important to bear in mind that it is an affection which seems to dispose to the development of cranial osteogenic sarcoma. For more details see page 663.

CHOLESTEATOMA

Particularly in the temporal bone, cystlike areas of epidermal origin arise in the diploe; at times epithelium and hair may be found within these cysts. Cholesterin crystals are usually present which prompted Johannes Müller (1838) to give them the name *cholesteatoma*. The fact that they may give rise to localized osteolytic areas, often multilocular, which encroach upon both the inner and outer tables, forces us to mention them since they must be considered in the diagnosis of single lytic bones lesions in the skull. These rarefied areas may be surrounded by a peripheral zone of increased density.

OSTEOPOROSIS CIRCUMSCRIPTA

This early cranial manifestation of Paget's disease gives rise to a sharply defined area of lessened bone density which may simulate a destructive metastatic lesion. In such cases, the alkaline serum phosphatase is usually not appreciably elevated. The process is, however, either slowly progressive or relatively stationary and symptomless (see page 670).

HYPEROSTOSIS FRONTALIS INTERNA

The existence of this peculiar localized sclerosing lesion should be borne in mind in connection with tumors of the skull. Its etiology is unknown. The appearance of the lesion on roentgenograms is quite distinctive and should not occasion any special diagnostic difficulty.

42. TUMORS OF THE JAW BONE

THEORETICALLY ALL TYPES OF BONE TUMORS, BOTH BENIGN AND MALIGNANT, may occur in the jaws. Metastatic foci from distant primary cancer of any part of the body may find lodgment there. Bone destruction from direct invasion from intraoral cancer or from cervical-node metastases is relatively frequent. There are certain varieties of primary bone tumors which are prone to occur in or are peculiar to this location while others are seen but rarely, if at all.

Since the treatment of many of these jaw tumors is highly specialized, calling for particular care in the pre- and postoperative management and for modifications in the administration of anesthesia, it is well to consider them separately. Those tumors which invade bone from primary sources within the oral cavity belong in the field of oral surgery or "head and neck" surgery and will not be described in detail here. Primary bone tumors of the jaw bone may, on the other hand, be of interest to those chiefly concerned with the general subject of bone tumors. In addition there is a group of tumors of dental origin which must be considered.

CLASSIFICATION

A convenient grouping of the more frequently encountered tumors of the jaws which arise from bone or within bone is as follows:

BENIGN	MALIGNANT
Fibroma	Fibrosarcoma
Fibrous dysplasia	Osteogenic sarcoma
Osteoma	Chondrosarcoma
Chondroma	Adamantinoma (rare)
Dentigerous Cyst	Carcinoma involving jaw bones
Epulis	by direct extension
Giant cell tumor	Metastatic tumors
Adamantinoma	

BENIGN GROUP

FIBROMA

Two forms of fibroma may occur in connection with the jaw bones. The process may present as a nodular projection which is attached to the bone

by a broad base and is similar to fibroma arising from the periosteum of bones in other localities. It is a slowly growing lesion and when first seen may have been present for years, causing the patient little inconvenience. The treatment consists in conservative excision or resection of the affected area.

The second and more frequent variety is often called ossifying fibroma as suggested by Montgomery, or fibrous osteoma according to Phemister and Grimson. The latter authors, and Eden as well, believed that this condition was related to membranous bone in a manner similar to that which osteochondroma bears to cartilaginous bone. These patients usually complain of facial asymmetry or difficulty with occlusion of the teeth. The superior maxilla is more often involved than the mandible, although occasionally both jaws are affected. The nose is not involved—a point that is of value in differentiating it from leontiasis ossea and some of the diffuse hyperostoses. There is no lymphadenopathy. There is a tendency to a gradual deceleration of growth so that the condition may become stationary in adult life.

Several authorities, notably Lichtenstein, Mallory, and Schlumberger, have recently called attention to the possible close relationship of this process to fibrous dysplasia. The author, on the other hand, considers that it may be misleading to accept the opinion of pathologists (based on the striking histologic similarity of these fibrocystic lesions), that they all represent a single disease entity.

Sherman and Sternbergh have recently reviewed a group of 11 cases of ossifying fibroma of the jaw bone from a roentgenographic standpoint. Pathologic material and clinical records were adequate in all of these cases. They were particularly concerned with the earliest available roentgenograms in each case. In 6 instances the mandible was involved, and in 5 the maxilla. Emphasis is laid on the fact that no cases have been reported save in these locations; these authors have not seen lesions in any other location which present a similar roentgenographic appearance: In every instance the tumor was monostotic. Those occurring in the mandible were medullary in character and were situated in various portions of the bone. The process is essentially destructive in the early stages but possesses a tendency later to exhibit productive changes. The lesion usually remains medullary and expands the bone in all directions equally. Periosteal reaction is conspicuously absent. Tooth displacement, especially in the mandibular cases, is commonly seen although variable in degree.

In tumors of maxillary origin the nares, orbit, and antrum may be involved; less often the anterior ethmoid cells may be encroached upon. Cortical expansion is regularly seen and may reach an extreme degree with marked thinning. Sherman and Sternbergh noted a tendency in the long-

standing cases to the formation of a thin bony periphery about the advancing margin of the tumor. These authors have marshalled a considerable number of facts which would indicate that from the roentgenographic standpoint at least, this condition is distinct from fibrous dysplasia occurring in the mandible or maxilla. Moreover the endocrine disturbances and pigmentation seen in the matured cases of fibrous dysplasia have never been observed in ossifying fibroma.

Treatment

Since extensive resections result in considerable disfigurement, most authorities recommend conservatism, although recognizing that these tumors tend to recur if incompletely removed and that therefore repeated operations and even complete jaw resection may eventually be required. Nevertheless, the conservative approach is considered justified since there are apparently no recorded cases of malignant alteration.



FIG. 248. Fibrous dysplasia of mandible.

FIBROUS DYSPLASIA

There is a surprising incidence of monostotic fibrous dysplasia lesions in the jaw. Schlumberger in a series of 67 cases found 7 in the superior maxilla and 2 in the mandible. This lesion must be taken into consideration when dealing with tumorlike processes in the jaw bones which give rise to circumscribed areas of radiolucency (see Fig. 248). When the presence of fibrous dysplasia of the jaw bones is suspected it is justifiable to operate with a view to obtaining an immediate frozen-section diagnosis. If this confirms the suspicion then a thorough curettage rather than a jaw resection is indicated.

OSTEOMA

This benign tumor composed of adult bone affects the maxilla more often than the mandible; it is rarely seen in the latter. Circumscribed, painless, and of slow growth, it is readily differentiated from most other jaw neoplasms by its roentgenographic appearance and its history of long duration.

Figures 249 and 250 illustrate a case involving the condyloid process of the mandible of a German prisoner of war whose face was unilaterally elongated with deflection of the chin to the opposite side, associated with pronounced malocclusion.

CHONDROMA

Like chondromas in other localities this tumor in the jaw may be either central or cortical in origin; it is usually circumscribed and not invasive.

Rarely does it attain large size. Most frequently it arises in the upper jaw of children and young adults. It is subject to the hazards of chondrosarcomatous alteration inherent in cartilage tumors in other parts of the skeleton.



FIG. 249. Osteoma of condylar area of right mandible. Note the facial asymmetry and the prominence over the superior portion of the mandible on the right side.

DENTIGEROUS CYST

The dentigerous cyst is a benign process consisting of a hollow cavity in the bone associated with an *unerupted permanent tooth*. While any tooth, even supernumerary ones, may be involved the most common are the canine and the mandibular third molar. The crown of the tooth usually lies exposed in the

cavity of the cyst while its root lies embedded in the cyst wall (see Fig. 251). The cyst itself is the result of proliferation and degeneration of cells of the enamel organ before the tooth erupts. The gradual increase in swelling of the jaw continues until the bone is so thinned that it presents the characteristic parchment-crackling sensation to the palpating finger, and fluctuation may at times be elicited. Roentgenograms reveal a radiolucent area with sharply defined edges and the unerupted tooth which is so essential to the diagnosis.

The treatment is simple for it involves merely removal of the cyst with its lining membrane and generally the offending tooth as well. However, once the correct diagnosis has been established the management of these cases may be transferred to the oral surgeon.

EPULIS (DENTOPERIOSTEAL CYST)

It is important at the outset to define the term *epulis*. Much confusion has arisen from its loose application in the past. It implies a growth or swelling on the gum, yet some writers have used the term to describe tumors belonging in the group of benign giant cell tumors occurring in the jaw. It is a term which should be applied to a circumscribed growth which derives from the alveolar ridge adjacent to the gingival margin of the teeth. It arises from the dental periosteum often by a narrow pedicle and as it spreads over the gum surface it may displace or overlies the teeth. The term *dentoperiosteal tumor* or *marginal tumor* is probably more appropriate. Its close relationship to the inflammatory or infectious granulomata is

stressed by some pathologists who question its inclusion among the true tumors.

Giant cell epulis or marginal tumor of benign giant cell type is not rare.



FIG. 250. Osteoma of head and neck of mandible. (Same patient as Fig. 249.) Shows distortion of mandible that produced a marked facial asymmetry and malocclusion. The external swelling was great in proportion to the size as seen on the radiogram. (Glennan General Hospital.)

It presents a smooth, reddish, or violaceous swelling on the surface of the gum which is usually soft and compressible. It is not seen before the age of six, and usually corresponds in time and site to the shedding of deciduous teeth. It shows a tendency to increase in size and to displace or loosen adjacent teeth. The microscopic appearance of the tissue is identical with that found in giant cell tumor of other bones. These tumors may be sessile and extend along the gum between teeth, which may become loosened, or they may grow as a pedunculated process arising from a relatively narrow stalk. Two histologic types are recognized although they are not clearly of different origin. These are the giant cell epulis and the fibrous epulis. The majority are of fibroblastic type but contain multinucleated giant cells, some round cells, and at times myxomatous areas. In some instances these growths are of marked vascularity.

Treatment

Since incomplete removal is usually followed by recurrence it is essential to remove not merely the neck of the tumor but its base as well. To



FIG. 251. : Dentigerous cyst.

do this effectively it is considered necessary by Blair and Ivy, Padgett, and others, to extract at least one tooth and sometimes two. If this is done it affords a better opportunity to remove the dental periosteum from which the tumor arises. When it is difficult to decide which tooth is affected both should be extracted.

Under local infiltration or block anesthesia an incision is made through adjacent normal gum and carried down to bone. Through this incision the soft part attachments of the growth are freed and the suspect tooth is extracted. The epulis may thus be withdrawn since it is usually firmly attached by dental periosteum to the neck of the tooth. The bony edges of the socket are smoothed with a rongeur and iodoform gauze is placed over the raw exposed surface. Cauterization with the actual cautery is preferred by some surgeons.

Blair and Ivy do not advocate radium as a means of destroying these tumors because of its untoward effect on adjacent bone and mucous membrane.

BENIGN GIANT CELL TUMOR

If one excludes all cases that properly belong in the epulis group, true benign giant cell tumors arising within the mandible and not associated with dental periosteum are very rare, in fact at least one authority even questions their existence.

Unlike the epulis form—described above—true giant cell tumor may arise from the central portion of the bone and cause the typical expansion which is characteristic of this disease in other localities. It presents a relatively asymptomatic, slow-growing swelling of the alveolar portion. However, unless the cortex is broken through, the diagnosis may not be certain, as adamantinoma may present a roentgenographic appearance indistinguishable from that of giant cell tumor. Indeed, the incomplete removal of adamantinoma undertaken under the impression that the lesion is a giant cell tumor undoubtedly is responsible for the recurrences and the ultimate failure to control the disease in many cases. If it is technically practical an aspiration biopsy may be relied upon to establish the diagnosis before resorting to surgery.



FIG. 252. Adamantinoma. Successfully treated by resection of mandible.

Surgical extirpation is the method of choice. The preferred approach is through the skin overlying the jaw rather than through the mouth; this permits primary closure with little risk of subsequent infection. A jaw resection should seldom be necessary.

The prevalence of cystic lesions in the jaws due to hyperparathyroidism *should* prompt one to examine the serum calcium and to make a roentgenographic examination of the other bones in cases of suspected giant cell tumor of the jaws.

ADAMANTINOMA (AMELOBLASTOMA, ADAMANTINE EPITHELIOMA, ODONTOMA)

Adamantinoma is a primary tumor derived from epithelium of the enamel organ. It is essentially benign but potentially malignant. It is most prevalent in young adults, the majority of cases occurring in the age group of from 15 to 35 years, and in the colored races rather than in the white. The mandible is affected much more frequently than is the maxilla. The slow rate of growth is a striking feature, and cases in which the disease has been present for three or four decades are not unusual. Pain is not prominent and the chief complaint is progressive deformity of the face. The tumor extends outwards, presenting a prominent swelling of the jaw which may later bulge into the mouth, partly fill the buccal cavity, and eventually in-

terfere with mastication and even deglutition (see Figs. 252 and 253). The growth gradually erodes and expands the bone producing a shell of variable thickness. In the late stages it may be associated with ulceration of the



FIG. 253. Adamantinoma of mandible. Advanced, neglected case.

buccal mucosa and the development of a sinus infection as well as other mild secondary infections with seropurulent discharge.

Röntgenographic Features

The typical adamantinoma presents a mono- or polycystic central process of radiolucency which is sharply circumscribed and lacks a reactive bone margin or an irregular eroded edge such as is seen in carcinoma invading bone. It must be differentiated from dentigerous cyst, from the epulis or giant cell tumor of the jaw, and from areas of fibrous dysplasia.

Microscopic Appearance

The histologic picture is variable. The tumor may be solid in some areas and cystic in others. Originating from undifferentiated basal cells it may resemble adenoid cystic basal cell epithelioma (see Fig. 254). It is sometimes possible to demonstrate the differentiation of enameloblasts. Despite the usual preponderance of epithelial elements, at times much stroma is present which has the appearance of primitive mesenchyme. In such cases

as combine the cellular elements of dentine and enameloblasts and contain calcific material, the term *odontoma* has been employed. Kegel has concluded that the *adamantinoma* is derived from the inner layer of the enamel organ and assumes a relationship to cells of aberrant tooth germs.

Treatment

Curettage followed by cauterization is considered by Geschickter and Copeland to be the method of choice. The marked tendency to recurrence and the great difficulty in eradicating the disease once a recurrence has taken place has prompted surgeons to perform resection of the affected portion of bone whenever cases are encountered that have not previously had incomplete operation. Resection seems preferable to curettage and chemical cauterization. Because of the radioresistant nature of the tumor, radiation therapy offers nothing. If heavy exposures of roentgen rays are employed the likelihood of radiation osteitis is great. In the series reported by Kegel, 79 per cent recurred following curettage, while radiation therapy tried in 6 cases at Johns Hopkins was not successful.



FIG. 254. Histologic features of adamantinoma. (Section from case shown in Fig. 255, p. 438.)

Prognosis

Complete surgical extirpation is curative. Repeated unsuccessful surgical measures usually result in wide local recurrences. We have observed one case in which the *squamous* portion of the temporal bone was pushed in and indented by a recurrence. Metastasis is rare. Simmons had a case (reported by Thoma) with metastases to regional lymph nodes. We treated a case which we regard as of sufficient interest to warrant the following brief summary:

Case Report

M.McG., female, age 55 years, first noticed a swelling of the jaw at the age of 19. This was operated upon at Presbyterian Hospital in 1907. A recurrence followed and a second operation was performed at the same hospital in 1910. The patient remained *symptomless* for fourteen years when another recurrence took place in two separate areas. During the next six years it grew to the size shown in Figure 255 which was the appearance presented at the time of our first examination. Beginning in 1931 and extending through 1938 five more operative procedures were carried out. Death took place on Feb. 3, 1939 or forty-eight

years from the time the tumor was first discovered and thirty-two years after the first operation.

Autopsy revealed metastases—typical of all previous operative specimens—to



FIG. 255. Recurrent adamantinoma. Showing appearance twenty-four years after the first operation and immediately prior to the third. Note that tumor presents as two masses, one in the temporal region, and the other in the right side of the lower jaw. (See case history, p 437.)

parietal and visceral pleura, liver, and kidneys. Death was due to a subdural frontal abscess.

ODONTOMA

The distinguishing feature of this tumor is its cellular composition which is a mixture of connective tissue derived from the dental papilla and epithelium of the enamel. Sheets or strands of epithelium similar to those seen in adamantinoma occur in odontomas but are subordinate to the mesenchymal tissue. The softer odontomas are less differentiated and are composed of connective tissue with myxomatous features as well as epithelium such as is found in adamantinoma. Their clinical course is that of an adamantinoma and lies between that tumor and the hard or more highly differentiated odontoma. The latter may arise either from elements that are associated with an unerupted tooth or from accessory tooth germs adjacent to the unerupted tooth. Viewed in the roentgenogram the unerupted tooth is seen lying in a mass of irregularly calcified material which occupies a

well circumscribed, expanded area of lessened density. The calcific material presents as dentine, enamel, and cementum lying in a matrix of cellular connective tissue. There is a tendency on the part of these calcific bodies to take on the appearance of imperfectly formed teeth.

The treatment of the hard odontomas may be more conservative since they exhibit a more definitely benign nature and do not recur after surgical extirpation. The soft odontomas, however, are infiltrating and more aggressive, and often recur.

Winter, Lifton, and McQuillan have recently reported a case in which they embedded a vitallium mandibular prosthesis after a wide removal of a portion of the mandible for adamantinoma. Their ingenious management of this difficult situation should encourage others to attempt similar operations in cases where bone transplants are not practical as a substitution for the resected portion of the mandible.

MALIGNANT GROUP

We have not attempted to segregate those osteogenic sarcomas of the jaw bones which might properly be termed *fibrosarcoma*, although some of the cases under consideration would unquestionably fall in this group. Chondrosarcoma also is considered together with osteogenic sarcoma because of its close similarity in clinical course, response to treatment, and prognosis.

While theoretically sarcoma of the jaw bone might develop on a pre-existing fibrous dysplasia—this has been described in connection with other bones—as far as we are aware there is no record of this transformation taking place in the mandible or maxilla.

SARCOMA OF JAW

The comparative infrequency of sarcoma of the jaw bones is evident from the paucity of case reports in the literature and is confirmed by the fact that in an eighteen-year period at Memorial Hospital only 35 histologically confirmed cases were seen on the Head and Neck Service.

Sex apparently played no important part in this series as shown by the following figures: 18 males and 17 females. The average age was 36; the youngest patient was 6 and the eldest 66 years.

The type of sarcoma noted in these 35 cases was as follows: osteogenic sarcoma 19, chondrosarcoma 13, and 3 merely classified as sarcoma.

Swelling, pain, and disturbed mastication were the most frequent complaints. The average duration of symptoms was ten months, with a minimum of one month and a maximum of eighty-four months.

In trying to arrive at a diagnosis, the symptoms ought to indicate the need for a roentgenographic examination; in turn the films should suggest

the probability of a malignant tumor, and a biopsy or resection should furnish the pathologist with sufficient information to permit of a definite diagnosis (see Fig. 256).

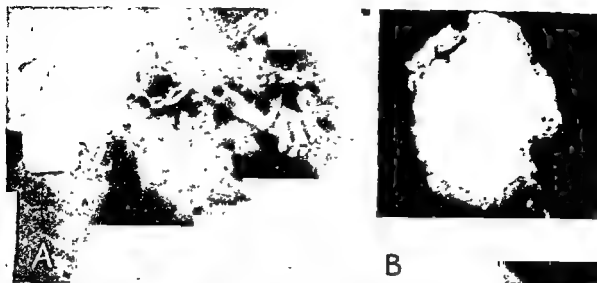


FIG. 256. A, Osteogenic sarcoma of mandible. B, Roentgenogram of resected specimen.

Treatment

Following a prolonged trial of various combinations of radiation therapy with or without surgery it is considered that radical jaw resection for osteogenic sarcoma is the method of choice. Cases receiving intensive irradiation yielded unsatisfactory results because the growth was not completely controlled and when surgery had to be employed the effect upon wound healing was unfortunate, bone necrosis, sloughing, and secondary infection ensued and the end results were deplorable.

In the Memorial Hospital series 18 patients were treated by irradiation and surgery, 13 by surgery alone, and 3 by irradiation alone.

In 16 of the cases that are known to be dead, the following treatment was administered: irradiation alone in 3, surgery alone in 3, and a combination of irradiation and surgery in 10 cases. All died of sarcoma with the exception of one who succumbed to a pulmonary abscess.

In 18 cases that are known to be alive, 10 were treated by surgery alone and 8 with a combination of surgery and irradiation; none received irradiation alone. One other patient received no treatment at all.

Prognosis

The ultimate outcome in sarcoma of the jaw is dependent upon the stage at which treatment is instituted, the aggressiveness of the surgical removal, and the histologic character of the tumor. In 15 fatal cases, eight died while the disease was still localized, four had pulmonary metastases, two had severe local radiation necrosis, and one succumbed to a pulmonary

abscess. One patient is living sixteen years after treatment. Twenty-two cases are summarized in Table XXXV.

TABLE XXXV
FIVE-YEAR END RESULTS IN TWENTY-TWO CASES OF SARCOMA OF JAW*

INDETERMINATE GROUP:	CASES
Dead as a result of other causes, without recurrence	1
DETERMINATE GROUP:	
Failures: Dead as a result of sarcoma	13
Refused treatment, presumed to be dead	1
Successes: Free of disease after 5 years	7
	<hr/>
Five-year survival rate based on determinate group	33.3%

*From Memorial Hospital 1929-1942. Courtesy of Dr. Hayes E. Martin. Head and Neck Service, Memorial Hospital.

ADAMANTINOMA

Because in a small but appreciable percentage of cases adamantinoma behaves like a malignant tumor, giving rise to metastasis to the adjacent lymph nodes or to distant parts by way of the blood stream, it deserves mention among the malignant neoplasms of jaw bones.

BONE INVOLVEMENT BY DIRECT EXTENSION FROM CARCINOMA OF THE ORAL CAVITY, NASOPHARYNX, AND ACCESSORY SINUSES

Epithelial cancers of the buccal mucosa, palate, floor of the mouth, tongue, lip, and salivary glands may invade the mandible or maxilla by direct extension. In such circumstances the problems which are presented are grave although the diagnosis is usually not difficult. Some conception of the extent of the bone involvement can be gained from a roentgenogram.

The treatment depends upon a number of factors which include the extent of lymph-node involvement, the operability of the primary growth, and the feasibility of jaw resection. Tumors of marked radiosensitivity are uncommon in this group but when they do occur they may be treated by irradiation. This form of therapy is also of use as a palliative measure in cases that are not considered operable. But whenever the clinical setting is favorable for surgery this is the method of choice.

METASTATIC TUMORS

When a tumor or cyst is encountered in the maxilla or mandible the possibility that it may be a metastatic lesion must be borne in mind, although these bones are only infrequently involved. Primary bone sarcoma with metastasis to the jaws is uncommon. Ewing's sarcoma provides the majority of these cases. Osteogenic sarcoma has produced such secondary deposits in only one or two instances in our experience. Metastasis from carcinoma is also rare. Ivy has reported a case in the mandible which was derived from the so-called "benign metastasizing struma." This tumor is actually

an adenocarcinoma of the thyroid. A similar case is under the author's care in which a thyroidectomy had been performed seven years previously. If the existence of a primary tumor is known, the diagnosis ought not to be difficult. It can be confirmed by aspiration biopsy.

The treatment is purely palliative. Roentgen therapy is the method of choice. In exceptional circumstances resection may be considered for the relief of pain. The ultimate prognosis is hopeless regardless of the method of therapy employed.

43. TUMORS OF THE THORACIC WALL

BENIGN AND MALIGNANT TUMORS OF THE RIBS, COSTAL CARTILAGES, AND sternum are uncommon if metastatic carcinoma and plasma cell myeloma are excluded.

Hedblom collected 313 cases from the literature prior to 1933 and Sommer and Major added 81 cases from 1933 to 1942 (see Table XXXVI). Some

TABLE XXXVI
TUMORS OF THE THORACIC WALL*

	RIB	STERNUM
Osteoma	5	0
Chondroma	14	2
Benign giant cell tumor	9	0
Osteogenic sarcoma	18	2
Ewing's sarcoma	18	0
Fibrosarcoma (bony origin uncertain)	6	0
Unclassified	5	0
Hodgkin's disease	1	3
Lymphosarcoma	2	0
Miscellaneous tumors	3	0
	81	7
Hedblom's collected cases prior to 1933		88 313
Total collected cases to 1942		401

* SOMMER, G. N. J., JR., and MAJOR, R. C. Neoplasms of bony thoracic wall
Ann Surg 115 51, 1942

idea of the relative frequency of sarcoma in this region may be gained from the following figures: Campbell found 1 rib case in 57 osteogenic sarcomas; Meyerding found 3 rib and 3 sternal cases in 100 osteogenic sarcomas (see Fig. 257). Desjardins, Meyerding, and Leddy reported 1 rib case in 42 Ewing's sarcomas, and Campbell 1 rib case in 23 Ewing's sarcomas. The disparity between rib and sternal tumors is shown by Sommer's and Major's figures of 81 rib and 7 sternal cases, a proportion of 11 to 1.

Central chondroma is the commonest benign form and of great importance because of its tendency in middle or late adult life to undergo chon-

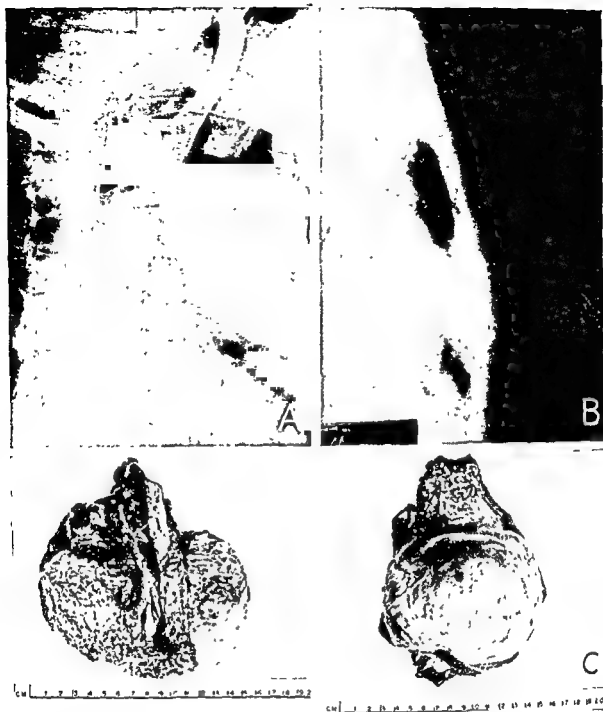


FIG. 257. A, Chondrosarcoma of sternum. This patient had a benign chondroma for at least thirty years prior to resection of the body and ensiform of sternum. B, Lateral view of sternum in same case C, Gross specimen. The glistening surface represents the intrathoracic portion covered with parietal pleura.

drosarcomatous alteration. It may arise in the rib itself or in connection with costal cartilages, and occasionally in the sternum (see Fig. 258). When discovered while still localized and quiescent, excision or resection is advisable; once it has begun to grow in size and to give rise to symptoms it is usually already malignant.

Giant cell tumor is quite unusual in the ribs and virtually unknown in the sternum. No case was found in this latter location in 124 cases in the author's collection from Memorial Hospital and Hospital for Special Surgery.

Ewing's sarcoma (endothelioma of bone) may involve the ribs but is exceedingly rare in the sternum (see Fig. 259).

Fibrous dysplasia, bone cyst, eosinophilic granuloma, and osteoid osteoma are other infrequent lesions that may occur in the ribs. Tietze's disease may also arouse suspicion of a rib tumor (see p. 700).

Metastatic cancer and plasma cell myeloma comprise the vast majority of destructive rib tumors although the former is surprisingly seldom responsible for sternal involvement.

Other conditions which may require consideration in establishing a diagnosis of thoracic wall tumors are osteomyelitis, gumma, cold abscess, aneurysm, mediastinal tumors, echinococcus cyst, empyema necessitatis, and bronchial carcinoma.

TREATMENT

Modern refinements in the field of anesthesiology have greatly increased the scope of and contributed to the safety of surgical attack upon tumors of the thoracic wall; postoperative complications have likewise been reduced.

Complete surgical extirpation of the tumor-bearing portion of the rib is the most satisfactory measure available. It is possible that with more aggressive attack at an earlier stage of the disease more successful end results may be attained.

For benign rib tumors partial resection of the involved rib, transecting it wide of the diseased area, is sufficient. Malignant tumors demand a more



FIG. 258. Chondroma of rib. This was completely resected and patient had an excellent result when seen one year later.

extensive procedure. It has been our practice to resect the affected rib together with the one immediately above and below it from the costal cartilage to a point near the vertebral end. This removal of the block of



FIG. 259. Endothelioma of right ninth rib.

chestwall permits closure of the defect in layers and the lung can then be inflated before the final sutures are placed. Postoperative collections of fluid should be aspirated and collapse of the lung thus prevented.

Removal of a large part of the sternum for primary sarcoma or for extensive presarcomatous chondroma is entirely feasible. Tantalum replacement of the resected portion was successfully employed in a case seen in an Army hospital. In a personal case, a wide fascia lata graft was used to cover the defect and the result was entirely satisfactory.

Prior to reaching a decision regarding operation, roentgenographic study after preliminary artificial pneumothorax may give valuable information since many thoracic wall tumors invade the pleura and may even extend into the lung. Churchill has reported a unique case in which successful lobectomy was performed for a hematogenous metastasis to the right lower lobe from a primary sarcoma of a rib. Roentgen therapy has a definite place

in the palliative treatment of many tumors of the chestwall; the more radio-sensitive the type, the more striking will be the relief obtained.

PROGNOSIS

The ultimate outlook for all malignant tumors of the thoracic wall is exceedingly unfavorable. Our records reveal but a single case of rib sarcoma that has survived five or more years. None of the 20 cases of osteogenic sarcoma or 18 cases of Ewing's sarcoma reported by Sommer and Major were known to be well five years.

44. TUMORS OF THE PELVIC BONES

PRIMARY TUMORS OF THE PELVIC BONES ARE NOT SO COMMON AS ARE metastatic tumors, which have a predilection for the axial skeleton. *Benign tumors of the pelvis are less accessible to surgical removal, and malignant growths are also less frequently operable than are those situated in the long bones. The diagnosis of a suspected lesion is more difficult in the pelvic bones than in the tubular long bones because the roentgenographic criteria are less clearly defined in flat bones. It is therefore not always easy to determine whether one is dealing with a benign or a malignant tumor, or whether it is primary or metastatic. The ultimate decision must in many cases depend upon the histologic interpretation. Open biopsy is not always an innocuous procedure in lesions of the pelvic bones; it may seriously interfere with subsequent attempts to extirpate the growth or to treat it by radiation. Consequently aspiration biopsy is a valuable procedure in such cases.*

Every variety of bone tumor may be found in the pelvic bones although the incidence is distinctly lower for all forms of primary bone sarcoma than for the long bones. In our experience only 10 per cent of the osteogenic sarcomas, 13 per cent of the giant cell tumors, and 16 per cent of the endotheliomas have their origin in the pelvis. On the other hand, metastatic growths and multiple myelomas have a predilection for this site. In consequence it is to be noted that in a patient past the age of 35 a solitary destructive lesion in one of the pelvic bones is most apt to be metastatic or plasma cell myeloma, and multiple lesions are virtually certain to be due to one or the other of these diseases.

BENIGN TUMORS

Chondroma exceeds in frequency all other benign tumors of bone situated in the pelvis. Giant cell tumor is relatively common in this location while osteoid osteoma, nonosteogenic fibroma, and fibrous dysplasia are rare. Chondroma in this situation is an insidious and dangerous disease because,

owing to its comparative inaccessibility and its relatively symptomless and slow growth, it may extend widely in the bone and reach a considerable size before the patient seeks medical advice (see Fig. 260). Moreover, as

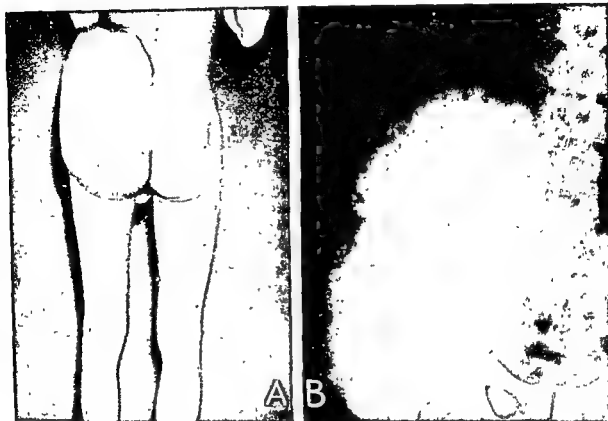


FIG. 260. A, Extensive osteochondroma of ilium in a 38-year-old male. Involvement within the pelvis and iliac fossa was very marked yet a hemipelvectomy was successfully performed and the patient is well fifteen months later. The pronounced tendency of tumors of this sort to undergo sarcomatous degeneration makes an attempt at complete extirpation mandatory. B, Roentgenogram of same patient.

in chondroma in other localities, there is a tendency to sarcomatous alteration. Whenever possible efforts should be made to remove the tumor as completely as is consistent with sound surgical principles.

Giant cell tumor in a pelvic bone, owing to its location and to the difficulty of obtaining hemostasis during curettage, is less amenable to surgical removal. Here the decision between surgical or roentgen therapy may be a difficult one to make (see Figs. 261 and 262).

Chordoma, a distinctly rare tumor, is of sufficient importance to warrant a special description (see p. 452).

MALIGNANT TUMORS

PRIMARY

Osteogenic sarcoma, Ewing's sarcoma, and plasma cell myeloma are sources of malignant pelvic tumor which may be considered as a group. In all, the outlook is exceedingly unfavorable.

The treatment of Ewing's sarcoma is best carried out with roentgen rays; plasma cell myeloma may also be temporarily benefited thereby.

Until *interilio-abdominal amputation* began to be more widely employed

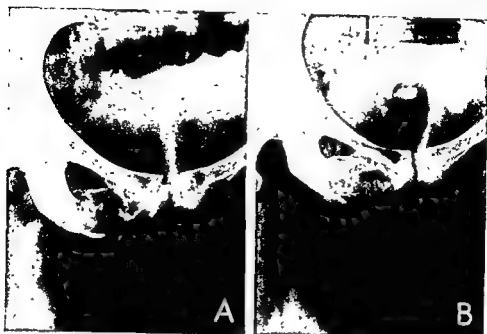


FIG. 261. A, Giant cell tumor of pubis. B, Appearance nine years later, showing healing following roentgen therapy.

and its operative mortality lessened, osteogenic sarcoma and chondrosarcoma were usually subjected to roentgen therapy with little prospect of more than mild and temporary alleviation of symptoms. Due to modern technical developments, especially in preoperative preparation, the use of massive blood replacement, refinements in anesthesia, and better post-operative care, the forbidding mortality rates of earlier times have been markedly lowered and the procedure is now much less hazardous although still formidable. Gordon-Taylor in England, and Morton, Sugarbaker, and Pack in America, have presented impressive personal series of recoveries. It is now an accepted and established procedure applicable to selected cases of malignant tumors of the pelvic bone, as well as those of the soft parts.

To us it has seemed particularly applicable in borderline or low-grade sarcomas of cartilaginous origin, especially of the ilium, where the lesion is reasonably circumscribed and not too great in extent. It may also deserve consideration as a palliative measure in cases which are thought to be incurable but where, because of slow growth and tendency to late metastasis, a prolonged and painful course is anticipated.

The ultimate success of hemipelvectomy (*interilio-abdominal amputation*) as determined by five-year survivals awaits the accumulation of a substantial number of carefully traced cases. We are aware of only 1 case,

i.e., that of Platt of Manchester, England, which involved a pelvic bone and was reported alive and well eight years after operation.

The only surgical alternative to hemipelvectomy is spinothalamic chlorotomy. This measure is worthy of serious consideration as a substitute in cases in which hemipelvectomy is obviously only a palliative procedure.

PLASMA CELL MYELOMA

In the majority of cases of plasma cell myeloma pelvic involvement is only a part of the visible skeletal disease. Cases are seen in which the pelvic lesion may be the only one demonstrable on roentgenographic examination of the entire skeleton. Some of these patients with "solitary" lesions in the ilium have been made comfortable for several years by roentgen therapy in moderate doses (1500-2000 r) given to the affected area.



FIG. 262. Giant cell tumor of ilium.

METASTATIC TUMORS

Prostatic carcinoma is responsible for the majority of cases of skeletal metastases to the bones of the pelvis. In spite of the absence of any urinary symptoms and any palpable evidence of cancer in the prostate itself one should suspect metastases from this source in a male over 50 years of age who presents the complaint of low-back or pelvic pain. If osteoblastic areas are seen in the pelvic bones the presumption is strengthened and a determination of the acid and alkaline phosphatase should enable one to establish the diagnosis. Paget's disease may present a somewhat similar appearance on the roentgenogram but in this condition, although the alkaline phosphatase is also elevated, the acid phosphatase is not increased proportionately as is the case with cancer of the prostate.

Solitary metastasis, osteolytic in type, is most often seen in the pelvic bones when the primary growth is in the thyroid or kidney.

Diffuse, lytic lesions are not common in breast cancer but usually the lumbar spine or upper femoral region also show signs of involvement.

It is essential that a complete roentgenographic examination of the entire skeleton be made whenever a pelvic bone lesion in an adult is discovered which might be construed as metastatic.

The treatment depends upon the source from which the metastasis arose. Hormone therapy for breast and prostatic metastases, and radioactive

iodine for selected cases of thyroid origin (based on the ability of the tumor to pick up iodine) are specific modes of attack that offer a prospect of considerable palliation. For other types of tumor, radiation therapy may be employed with the realization that the results, while unpredictable, may be worthwhile.

ROENTGEN THERAPY

Pelvic sarcomas of radiosensitive type, such as Ewing's sarcoma or reticulum cell sarcoma of bone, should receive roentgen therapy through available portals in doses considered sufficient to cause permanent inactivation of the tumor. Maximal doses compatible with maintaining the integrity of the overlying soft parts and skin are indicated for inoperable osteogenic sarcoma and chondrosarcoma. Metastatic carcinoma and plasma cell myeloma should not receive massive doses. Here the aim is relief of pain and control of the growth without complete inhibition of bone regeneration, the object being to secure maximal palliation without prospect of permanent cure.

CHORDOMA

The term *chordoma* is applied to tumors derived from the primitive notochord. They are characterized by slow but inexorably progressive growth, a tendency to invade and destroy bone by direct extension, to recur after repeated attempts at surgical removal, to resist irradiation, and in about 10 per cent of the cases to metastasize to lymph nodes, liver, lung, and other localities.

When Virchow, in 1857, first described small tumorlike masses near the clivus at the spheno-occipital synchondrosis, he observed that they were composed of vesicular cells surrounded by a matrix which simulated histologically the appearance of cartilage. He therefore called them *ecchon-drosis physaliphora* ("cartilage vacuole containing cells"). One year later Muller suggested their relationship to the chorda dorsalis, and added that "whosoever likes the name may designate these masses as chordoid tumors or chordomas." It remained for Ribbert, in 1894, to establish the true nature of these neoplasms by presenting 5 cases which he felt supported Müller's theory of their origin. His conclusions were based on the following observations: (1) The tumors seemed to have arisen from the midline of the clivus; (2) in no case could one demonstrate the transitional stage from cartilage to tumor; (3) the neoplasm and cartilage merely coexist side by side—a persistence of vestigial primitive notochordal structure; (4) in chordoma undergoing gelatinous softening the cells do not present the typical physaliphorus appearance with a mucinous substance between the

cell groups; (5) there was a definite resemblance between the histologic pattern of chordoma and that of notochordal vestiges in the intervertebral discs.

The first case of sacrococcygeal chordoma was reported by Hennig in 1900. The patient was a 7-months still-birth. Grahl, in 1903, recorded the first case of spheno-occipital chordoma. The first authentic case of vertebral chordoma, described by Raul and Diss (cited by Mabrey), was situated in the cervical region.

INCIDENCE

In the series of 55 cases of chordoma reported by Stewart and Morin in 1926, the distribution was as shown in the accompanying table.

TABLE XXXVII
DISTRIBUTION OF CHORDOMA

	NUMBER OF CASES
Sacrococcygeal	16
Cranial	1
Cervical	8
Occipital region	1
Upper and lower jaw	1
Thoracic	12
Lumbar region	7
	1

In 1935, Mabrey reviewed a group of 150 cases and found the distribution as follows:

REGION	NUMBER OF CASES
Sacrococcygeal	87
Cranial	49
Cervical	7
Lumbar	5
Thoracic	2

AGE AND SEX

Chordoma may occur at any age. Of the 128 sacrococcygeal cases reviewed by Gentile and the author, the youngest patient was 3 months old and the oldest 78 years, the average being 46 years. In general, it is a disease most often seen in patients over 50 years old.

Sex is of interest in that the condition affects males more than twice as often as females. In the series of 128 cases mentioned, there were 88 males and 40 females.

TRAUMA

A number of authors have suggested a relationship between trauma and sacrococcygeal chordoma. Mabrey noted a history of injury in 26 per cent of all sacrococcygeal cases. Fletcher, Woltman, and Adson reported 10 cases with a definite history of injury in 2. Bruce and Mekie maintain that "it is difficult to dissociate trauma and chordoma as to cause and effect."

In our review of the literature we found that 41 of 128 patients had suffered definite trauma to the lower end of the spine some time prior to the onset of clinical symptoms of the neoplastic process. This incidence, 32 per cent, seems rather high to be regarded as merely coincidental. Moreover, of the 41 cases with a traumatic history 33 were in males and only 8 in females, and the susceptibility of men to injuries in this region must be considered as greater than that of females. It seems significant that in intracranial chordoma, where the notochordal tissue is well protected from trauma, there is an absence of sex predominance. Bruce and Mekie note that injury would release notochordal tissue from situations where it is normally imprisoned in a fibrous envelope. We believe therefore that the possible relationship between trauma and chordoma, while not definitely proven, merits further consideration and study.

CLINICAL FEATURES

Pain in the lower spine or pelvic region is the chief and often the only presenting symptom. Because of the extremely slow growth, which may cover a period of years, patients do not seek medical advice early. In the 128 cases previously cited the average duration of symptoms prior to a medical consultation was twenty months; in 2 instances it was twenty years. Occasional cases have been reported in which the course of the disease became fulminating; Montgomery described 2 in which the duration was only one month and where death occurred shortly thereafter.

Physical Examination

The significant physical finding in a case of sacrococcygeal chordoma is the presence of a mass. If the tumor is located anteriorly and protrudes into the pelvis it may push the rectum forward and only by a digital rectal examination can the lesion be detected. A large sacral tumor can readily be overlooked if the examiner's interest is focused on the prostatic gland only. Its consistency may vary from firm to semicystic. Constipation may be the result of rectal pressure, and urologic complaints and neurologic signs may be observed.

Roentgenographic Findings

In cases where there has been actual bone destruction studies by means of roentgenograms may be useful (see Fig. 263). This tumor produces a

solid. (2) The presence of physaliphorous cells which are large and resemble bladder epithelium is an important finding (see Figs. 264-266). Sometimes individual cell demarcation is lost and the appearance is that

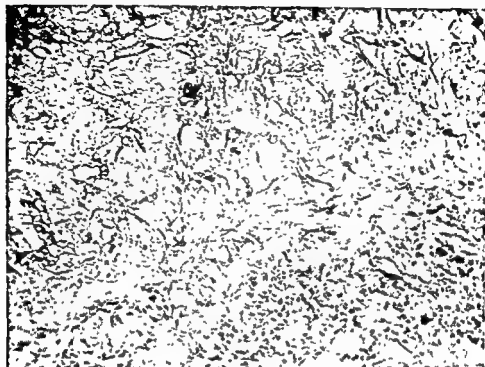


FIG. 264. Microphotograph of sacral chordoma.

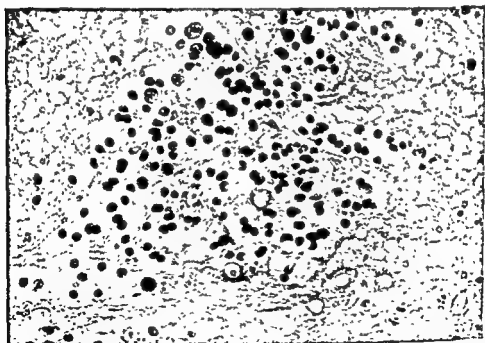


FIG. 265 Microphotograph of sacral chordoma. Note the physaliphorous cells.

of a highly vacuolated syncytium. (3) The tendency of the cells to grow in cords or to assume a lobulated arrangement.

Usually the criteria of benign, borderline or, at most, low-grade malignancy prevail in sections of aspirated tissue from chordoma.

TREATMENT

This is a most discouraging disease to treat by any method. The literature contains few reports of survival for long periods after radical surgery.

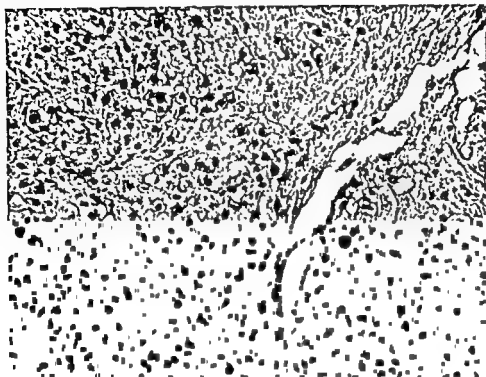


FIG. 266. Microphotograph of chordoma. Structure reminiscent of that seen in the primitive notocord.

Usually preoperative or postoperative irradiation has supplemented operative measures. Five of the 7 Memorial Hospital cases were given radiation therapy without surgery; 2 had surgical excision with preoperative roentgen therapy in 1 instance. We have only 1 patient alive more than five years after treatment.

Despite the difficulties and perhaps the impossibility of surgical extirpation, there seems reason to persist in attempts to devise better operative technics. Even palliative operations to remove painful recurrent tumors may afford much temporary benefit. The degree and duration of relief from pain after palliative roentgen therapy is seldom very impressive but one may nevertheless be entirely justified in using it.

In view of the long course of the disease, the ultimate agony of the patient, and the late development of distant metastases, these patients present a pitiable situation requiring either some palliative neurosurgical procedure, such as rhizotomy or preferably spinothalamic chordotomy, or long-term sedation.

It has been amply demonstrated that until a new, revolutionary method of operating on sacrococcygeal chordoma is devised and made practical, the patient who develops this long, drawn-out disease has little to look forward to in life.

45. TUMORS OF THE VERTEBRAL COLUMN

P RIMARY BONE TUMORS SELDOM ARISE IN THE VERTEBRAL COLUMN. Osteogenic sarcoma, Ewing's sarcoma, and reticulum cell sarcoma are extremely uncommon in this location. Plasma cell myeloma, having a marked predilection for red marrow areas of the skeleton, affects the vertebrae in a high percentage of cases, while metastatic cancer, particularly of breast and prostatic origin, likewise involves the vertebrae with great frequency.

Giant cell tumor is occasionally seen in the spine where, because of its tendency to cause expansion of the bone, it may give rise to serious symptoms of cord compression. Lewis states that Bloodgood in a collected series of 179 giant cell tumors (including his own as well as the Bone Registry cases) found 5 cases in which the vertebrae were involved. Lewis also reported 17 cases of vertebral giant cell tumor (including 1 of his own) in all of which there was histologic confirmation of the diagnosis. The ages ranged from 7 to 40 years. The location was as follows: cervical vertebra 1, dorsal vertebra 5, lumbar vertebra 7, sacrum 1, not stated 3. In none did the disease metastasize. There were some local recurrences, and 4 deaths. A complete removal was not attempted in any of these 17 cases.

Bone cyst of the spine is rare; we have observed it on only 2 occasions.

Chordoma is confined almost exclusively to the spinal column and nearly always to the upper cervical and sacral segments.

DIFFERENTIAL DIAGNOSIS

One must first decide whether a bony lesion of the spine is a tumor or some nonneoplastic condition. Among the latter are tuberculosis (Pott's disease), hyperparathyroidism, Hand-Schüller-Christian's disease in children, and osteoporosis in elderly subjects (especially postmenopausal osteoporosis).

If the lesion is considered to be a tumor it must be decided whether it is benign or malignant. Of the benign tumors, hemangioma and giant cell

tumor are likely possibilities and they may be readily distinguished by the roentgenographic appearance (see Fig. 48, p. 119, and Fig. 102, p. 186).

If it seems probable that the tumor is malignant the decision as to its being primary or metastatic must be made. The odds are overwhelmingly in favor of its being either plasma cell myeloma or metastatic cancer. Complete skeletal films should be made. If there are other areas found, primary bone sarcoma is eliminated, and sternal marrow puncture, plasma protein determination, and Bence-Jones test of the urine may establish whether it is myeloma or metastatic carcinoma. If the diagnosis is still in doubt a biopsy by means of aspiration is less hazardous than is an open surgical biopsy for tumors of the vertebral bodies and may yield satisfactory material for histologic interpretation.

TREATMENT

While the treatment of the various bone tumors of the vertebral column follows in general that outlined for such tumors occurring in other locations, there are certain difficulties which are associated with this locality which may make it necessary to adopt a different approach. To be more specific, owing to the great difficulty of a complete surgical removal of a tumor of the vertebrae, roentgen therapy rather than surgery has been the method more widely employed. Repeated attempts at extirpation resolve themselves into incomplete removals which are not of great benefit.

Roentgen therapy offers but little for osteogenic sarcoma or chondrosarcoma, two conditions that are very rarely primary in the spine. It may afford worthwhile palliation in plasma cell myeloma, and it may produce excellent results in hemangioma or giant cell tumor. There is no other practical method of local treatment of metastases to the spine save that of hormone therapy or castration for prostatic or mammary cancer.

The inability to predict the degree of worthwhile relief obtainable from roentgen therapy should not dissuade the clinician from giving it a fair trial in every case of spinal metastasis where the patient's general health permits. An exception should be made in the highly specialized tumor known as chordoma which is so radioresistant that we seldom treat it by irradiation. Benign tumors, which are confined to the processes (transverse and spinous) of a vertebra, may sometimes be successfully treated by surgical means. These include the cysts and giant cell tumors. It is possible that the scope of surgical measures may be extended in time by the combined efforts of the orthopedic surgeon and the neurosurgeon.

46. TUMORS OF THE HANDS AND FEET

TUMORS OF ANY TYPE RARELY ORIGINATE IN THE BONES OF THE HANDS AND feet. This is borne out by an extensive review of the literature as well as the statistics of Memorial Hospital. In a series of 10,459 cases of malignant disease occurring over a nineteen-year period, Schreiner and Wehr could find only 37 involving the foot; only 4 of these were bone sarcomas. Moore, in a survey of 1740 bone tumors at Johns Hopkins Hospital, found 46 benign and malignant tumors of the foot.

Since there are 206 bones in the entire skeleton, 106 of which are in the hands and feet, the disproportion in their relative frequency of involvement is apparent.

In a total of 1211 bone tumors at Memorial Hospital and the Hospital for Special Surgery (formerly the Hospital for Ruptured and Crippled), we found the bones of the hand involved in 20 instances and the bones of the foot in 27, making a total of 47 cases (Table XXXVIII). Six occupied the metacarpal bones and 14 the phalanges of the hand, i.e., 10 in the

TABLE XXXVIII
DISTRIBUTION OF TUMORS OF HANDS AND FEET*

	OSTEO- GENIC SAR- COMA	EWING'S ENDO- THELI- OMA	GIANT CELL TUMOR	CHON- DROMA	CYST	METAS- TATIC	ANGIO- SAR- COMA	TOTAL
Metacarpals	2		2	2				6
Phalanges 1	1		1	7	1			10
Phalanges 2			1	1				2
Phalanges 3					1	1		2
Astragalus								1
Calcaneus	3	4	3					10
Tarsals	1							1
Metatarsals	5	2	2				1	10
Phalanges 1				3				3
Phalanges 2				2				2
Phalanges 3								
	12	6	9	15	2	2	1	47

* From Memorial Hospital and Hospital for Ruptured and Crippled, observed up to January 1, 1917

proximal, 2 in the middle, and 2 in the distal phalanges. One tumor occurred in the astragalus, 10 in the calcaneus, and 1 in the cuneiform. Ten were found in the metatarsals and 5 in the phalanges of the foot (none in the proximal, 3 in the middle, and 2 in the distal phalanges). As to type, there were 12 osteogenic sarcomas, 7 Ewing's sarcomas (endothelioma), and 9 giant cell tumors. Exostoses and chondromyxomas are included among the 15 chondromas. There were 2 simple cysts, 2 metastatic lesions involving the bones of the hands and feet, and 1 angiosarcoma. Table XXXIX shows the distribution in 609 cases from the literature.

TABLE XXXIX
DISTRIBUTION OF TUMORS OF HANDS AND FEET*

	OSTEOGENIC	ENDOTHELIOMA	GIANT CELL TUMOR	CHONDROMA	MYXOMA	CYST	METASTATIC	EXOSTOSIS	OSTEOID OSTEOOMA	SARCOMA	TOTAL
UPPER											
Carpals		1				1		4			6
Metacarpals	2		11	7	1	7			1		29
Phalanges	2	1	9	54	7	16		12			101
Total (hand)	4	2	20	61	8	24		16	1		136
LOWER											
Astragalus	3		10	1	1	3			1		19
Calcaneus	21	21	17	4	1	7	1	205	1	1	279
Tarsal (other)	4		5	2		2	2	3		1	19
Metatarsal	3	6	9	7		5	2	3		3	38
Phalanges	2	2	4	16	1	6	2	84	1		118
Total (foot)	33	29	45	30	3	23	7	295	3	5	473
Total	37	31	65	91	11	47	7	311	4	5	609

*Cases collected from the literature

OSTEOGENIC SARCOMA

There were 12 osteogenic sarcomas in our series in addition to 37 in the literature. The symptoms noted were those found in osteogenic sarcoma in general, that is, pain in the involved region shortly followed by swelling and disability. There is a hard, palpable swelling which increases rapidly in size. The roentgenogram is typical, disclosing irregular bone destruction with laying down of new bone, often with a sunburst appearance. Aspiration biopsy is a valuable diagnostic aid and should be utilized to verify the clinical and roentgenographic findings. Many of these tumors are secondary to a benign chondroma and represent a malignant transformation of a simple chondroma into an osteochondrosarcoma. Not infrequently trauma is the alleged cause of this transformation. In other instances the tumors are of the fibrosarcoma type, and these apparently offer a more hopeful

prognosis. Five of our patients are alive and well, 3 for more than five years; 4 died of pulmonary metastasis from one to three years after admission; and 1 died following a prostatectomy performed nine years after his foot had been amputated for osteogenic sarcoma. One of the other 2 untraced cases is undoubtedly dead since he had pulmonary metastasis six months after treatment. From this five-year-survival rate, i.e., 33 per cent, it would appear that osteogenic sarcoma of the bones of the hands and feet

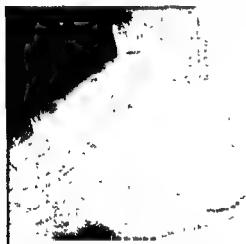


FIG. 267

FIG. 267. Osteogenic sarcoma of os calcis in a 15-year-old female. Amputation below knee followed by freedom from any evidence of disease for fourteen years.



FIG. 268

FIG. 268. Giant cell tumor of fourth metatarsal treated by resection of distal three-fourths of bone.

offers a more favorable prognosis than does the same condition in other bones (see Figs. 267-269).

TREATMENT

Once a diagnosis of osteogenic sarcoma has been made the treatment should be primary amputation. Local excisions and resections, with or without radiation, have been tried by others but without any five-year survivals to our knowledge. Partial amputations of the hand and foot may be justified, according to the extent and location of the lesion, thus leaving the patient with a functionally useful remnant, an impossible accomplishment when dealing with tumors of other parts of the skeleton.

ENDOTHELIOMA

Our series included 6 cases of this condition in addition to 31 in the literature. Here the onset is often indefinite and an erroneous diagnosis of

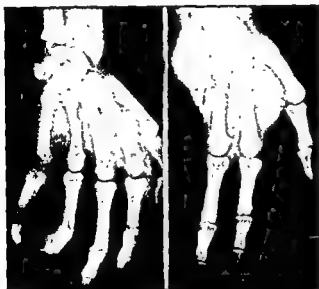


FIG. 269. A, Post-traumatic osteogenic sarcoma of proximal phalanx, apparently on a basis of ossifying hematoma. Osteogenic sarcoma involving a phalanx is exceedingly rare. There is no case on record in the Bone Sarcoma Registry. B, Same case one year after partial resection of hand. Patient, a bus driver, is working, and is free of disease ten years after operation.

chronic osteomyelitis is frequently made. Pain is the earliest symptom and is often accompanied by fever. The roentgenogram reveals bone destruction of a more or less diffuse nature but the fusiform shape and the periosteal splitting (features characteristic of this disease in the long tubular bones) are less frequently demonstrable. In this type also, aspiration biopsy is relatively simple and accurate, and should be attempted if there is any doubt of the diagnosis.

TREATMENT

The treatment here is surgical since heavy roentgen therapy in these areas (hands and feet) is hazardous. Amputation is the operation of choice. It may be followed by a course of toxin therapy (see p. 565).

GIANT CELL TUMOR

Our series contained 9 giant cell tumors in addition to 65 reported in the literature. Vague pain is usually an early symptom. Not infrequently, however, slight swelling or pathologic fracture is the first symptom. As these tumors are benign and grow relatively slowly they may attain a considerable size before the patient seeks medical relief. The roentgenographic appearance is usually quite characteristic, disclosing a round or ovoid, cen-

trally placed lesion with many fine trabeculations, usually well demarcated and with a thinned but intact cortex (see Figs. 270-273). The clinical and roentgenographic features are usually diagnostic. If the cortex is very thin,

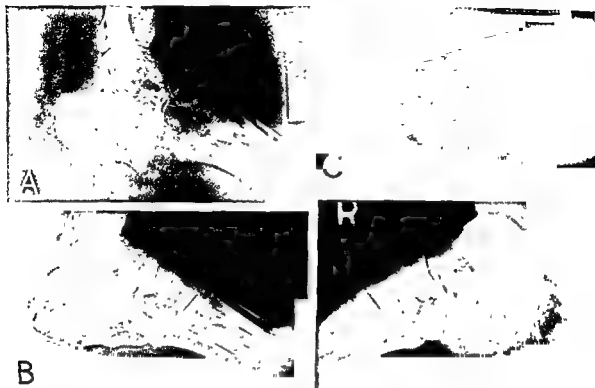


FIG. 270. A and B, Giant cell tumor of os calcis; C, two views of same case showing early improvement seven months after surgical treatment; five-year follow-up with excellent result.

an aspiration biopsy may be attempted but it is not so useful in this type of tumor. Following an extensive survey of giant cell tumors in general, we have come to the conclusion that the treatment of this condition is either surgery or irradiation but never both. For tumors located in the hands or feet, surgery is unquestionably the safer method.

CHONDROMA

Perhaps the commonest location for central chondroma is in the phalanges of the hand and, to a lesser extent, the foot (see Figs. 274 and 275). These tumors may be derived from pre-existing cartilage of congenital origin due to an abnormal anlage in the intermediate cartilage of the bone involved. In addition to the central chondromas, osteochondromas are also found in the phalanges and the metacarpals, and occasionally in the carpal bones as well (see Fig. 7, p. 12, and Fig. 276). They are often multiple, may be bilateral, and are at times responsible for marked deformities (see Figs. 277 and 278). The enchondromas, or central chondromas, pre-

sent themselves as cystlike areas of radiolucency and on the roentgenogram are often mistaken for cysts. They may have persisted for long periods without causing symptoms and indeed are seldom recognized until atten-

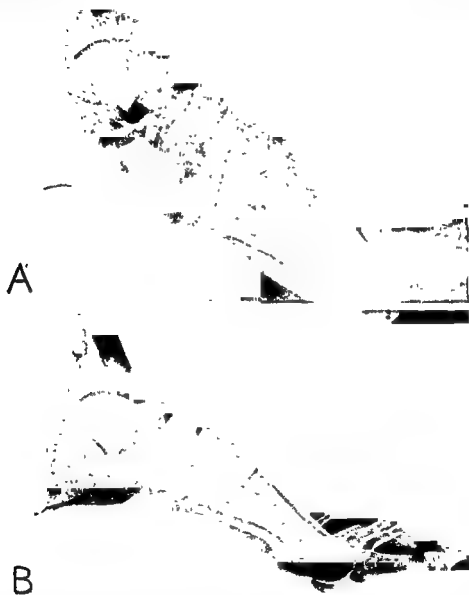


FIG. 271. A, Giant cell tumor of second metatarsal; B, appearance three years after curettage. Recurrence is growing in size. A second curettage was done, with bone chips to fill the cavity. A satisfactory result was obtained.

tion is called to them by reason of a minute cortical infraction or at times a frank pathologic fracture (see Fig. 279). The latter nearly always follows a trivial trauma (see Fig. 280).

The treatment of both enchondroma and osteochondroma of the hands is surgical. Small, symptomless osteochondromas may not require any treatment; larger or disfiguring ones should be removed as completely as pos-

sible. Central chondroma yields to curettage followed by cauterization with zinc chloride solution and filling of the cavity with match-stick bone transplants (see "Bone Cyst," p. 136).



FIG. 272. Low-grade chondromyxosarcoma of fifth metatarsal successfully treated by a partial amputation of the foot.

Subungual exostosis is a rare condition which probably should be grouped with osteochondroma. This condition is frequently associated with pyogenic granulomas of the great toe. In the literature they frequently appear under the diagnosis of exostosis. According to Davidson, the patient first notices that the nail is being slowly raised from its usual flat position, and then there appears a hard growth from beneath the nail which pushes it backwards. The growth increases gradually in size until the nail becomes almost vertical in its axis. Mason states that the condition is most common in the foot (usually in the great toe) and that there are only a dozen cases reported as occurring in the hand (usually in the index finger). The roentgenograms generally show a characteristic bony outgrowth but occasionally, if ossification has not occurred, they may be negative. Mason recommends removal with the least possible damage to the nail bed. Some authors favor removal of the nail and of the growth by means of chisel and

gouge, following this with cauterization of the base with phenol. Lapidus describes a more radical operation; employing a U-shaped incision, resecting the nail, and then resecting the distal half of the distal phalanx. He

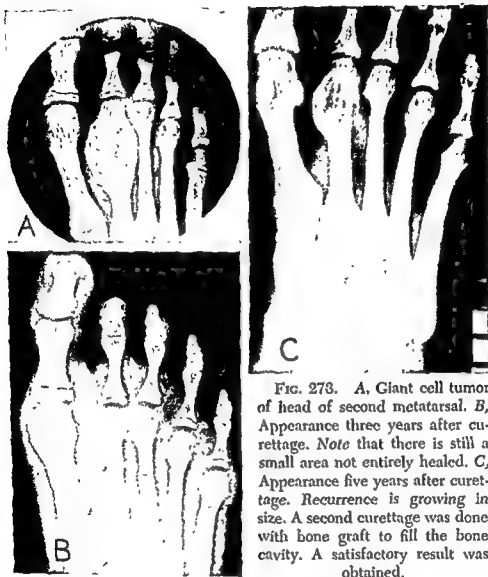


FIG. 273. A, Giant cell tumor of head of second metatarsal. B, Appearance three years after curettage. Note that there is still a small area not entirely healed. C, Appearance five years after curettage. Recurrence is growing in size. A second curettage was done with bone graft to fill the bone cavity. A satisfactory result was obtained.

uses a long posterior and a short anterior flap. Any of these procedures are acceptable, depending upon the size of the growth and the condition present in the individual case.

MYXOMA

Pure myxoma of the bones of the hands and feet is exceedingly rare. No case has been observed at Memorial Hospital. The symptoms, signs, and roentgenographic appearance closely resemble those found in chondromas and cyst. The differential diagnosis is difficult and is usually made on the histologic study alone. The operative or preoperative diagnosis is most important, however, since, as Kahn points out, these tumors require special treatment and are the most transplantable of all types. A thorough curet-

tage, followed by cauterization, is essential as these tumors are extremely prone to recur. In the event of the latter, Bloodgood advises an amputation. Not infrequently chondromatous and myxomatous elements are mixed



FIG. 274. Osteochondromatous changes in fourth and fifth fingers. Congenital.



FIG. 275. Central chondroma, the commonest bone tumor involving a phalanx.



FIG. 276. A, Enchondroma of terminal phalanx of thumb. B, Same case after curettage and bone chips.

in the one tumor, producing chondromyxoma. In Table XXXIX (p. 461) some of these have been included under *chondroma* and others under *myxoma*, according to the author's description. A predominance of the myxomatous element requires that the case be treated as a pure myxoma.

One must never lose sight of the fact that a chondroma, myxoma, or



FIG. 277. Multiple osteochondromatous changes in bones of the hand. The terminal phalanges appear to be unaffected. (Courtesy of Eastern Kentucky University.)



FIG. 278. Chondromatous involvement of fourth and fifth fingers.

chondromyxoma may undergo malignant transformation. Therefore no matter how minor the symptoms, we believe with Campbell that the tumor should be removed by operation at the earliest possible moment.

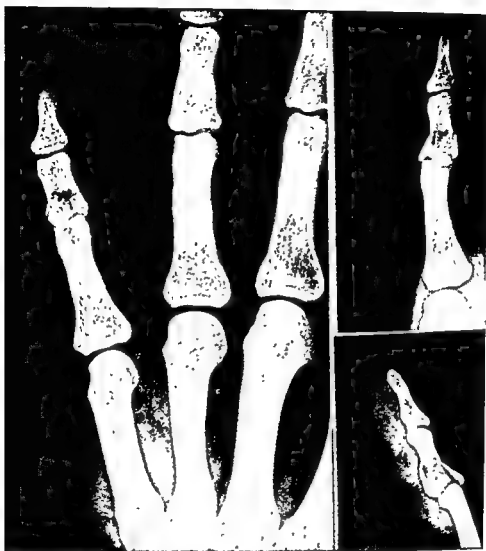


FIG. 279. Central chondroma of phalanx: Pathologic fracture was the initial symptom.

ANGIOMA

Rarely the small bones of the hands and feet may be the site of hemangioma. The roentgenographic appearance may be suggestive of this tumor but for a definite diagnosis histologic confirmation is desirable (see Fig. 281).

CYST

Simple cyst of the bones of the hands and feet is a most unusual condition. In many of reported cases, the diagnosis was based on clinical and roentgenographic evidence alone without histologic confirmation. We feel convinced that had pathologic material been studied in all of these cases not a few would have been transferred to the giant cell tumor or chondroma

group. As in central chondroma, pathologic fracture is usually the first symptom. The roentgenogram shows a small, rounded area of bone destruction with sharply defined margins. The trabeculations so characteristic of



FIG. 280. Chondroma. There is marked involvement of the little finger, less pronounced changes in the middle finger, chiefly medullary. The ring finger had been amputated previously for the same condition.

giant cell tumors are less prominent. Operation usually reveals a thin fibrous lining of the cyst wall containing clear yellow fluid.

The treatment does not differ from that prescribed for central chondroma.

METASTATIC CARCINOMA

Our series contains several cases of metastatic carcinoma involving the bones of the hands and feet (see Figs. 214, p. 381, and 217, p. 383). We have observed a deposit in the phalanx of a finger from a parotid tumor; the astragalus was affected in 1 instance from a hypernephroma and in another from a mammary carcinoma. In addition we have observed metastasis from the breast to the phalanges of the fingers and toes.

OSTEOID OSTEOMA

This condition has been described as occurring in the small bones of the hands and feet. Jaffe (1935) reported 3 such cases, and since then a number of others have been observed. The treatment does not differ essentially from that recommended for osteoid osteoma in other locations.

OTHER DISEASES OF BONE

The bones of the hands and feet may be involved in a number of generalized bone diseases. Thus, in Recklinghausen's osteitis fibrosa cystica



FIG. 281. Hemangioma of metatarsal bone.

(hyperparathyroidism) these bones may show manifestations of the generalized decalcification and cystic formation. A chondrodysplasia with multiple cartilaginous exostoses also may involve the bones of the hands and feet. In osteopetrosis (marble bones, Albers-Schönberg disease) one of the characteristic features of the early stages of the disease is the dense, banded appearance of the phalanges, metacarpals, and metatarsals. Paget's osteitis deformans also may extend to these bones, and it is conceivable that melorheostosis also may progress to below the wrist and ankle (see Fig. 378, p. 686).

Osteopoikilosis (spotted bones) is often found to affect the metatarsals, metacarpals, and phalanges. Giant cell tumors of tendon sheath origin (xanthomas) may by pressure produce bone changes that might arouse suspicion that the process arose from bone itself. The same may be said of synovioma which may occur in tendon sheaths or in joints of the hands and feet.

Bone destruction associated with gouty deposits in the feet may suggest a bone neoplasm although usually the true nature of the process is evident. We have observed a case in which the outline of the shaft of a metatarsal bone was altered by the presence of a tumor which at operation proved to be ganglion.

47. TUMORS OF BONE IN CHILDHOOD

FROM OBSERVATIONS AT MEMORIAL HOSPITAL AND ELSEWHERE IT IS EVIDENT that bone neoplasms comprise a prominent proportion of all new growths in the juvenile age group. Of 1770 cases of malignant tumors in children under the age of 14 years collected from several large series (including 576 from Memorial Hospital) 365 or 20 per cent were found in the skeletal system.

Of the primary malignant varieties, osteogenic sarcoma including chondrosarcoma, and Ewing's sarcoma (endothelioma of bone) comprise the vast majority; all others are exceedingly rare.

Of the many benign bone tumors encountered in children, osteochondroma and unicameral bone cyst predominate. Other lesions of bone which may simulate neoplasms include those due to infection, trauma, disturbed lipid metabolism, and the granulomas such as Hand-Schüller-Christian's disease, Letterer-Siwe's disease, and eosinophilic granuloma.

In children the diagnosis of bone sarcoma at an early stage is more difficult than in adolescents or adults, for the reason that up to the age of 6 or 8 years the child is a relatively uncomplaining individual and an evaluation of symptoms is often difficult. Lack of specific complaints therefore may have little meaning. In the preschool child the diagnosis must often be made from the objective findings rather than from the subjective symptoms. Obviously any child who does complain of pain of more than transitory duration ought to be thoroughly investigated. It should be borne in mind that bone sarcoma has an insidious onset, and that factors which are not as yet clearly understood affect the growth of bone and may influence the tumor as well. Any illness which fails to conform to the usual clinical course either at the onset or subsequently may be due to neoplastic disease.

A number of conditions most often encountered in childhood must be taken into consideration when making a differential diagnosis of bone tumor. Rheumatic infection gives rise to myalgias and arthralgias ("growing pains"). In cases of outspoken rheumatism no problem arises but in the low-grade rheumatic infections difficulty in diagnosis may be experienced.

Osteomyelitis due to pyogenic organisms usually is heralded by a sudden onset and the child is acutely ill. In such fulminating cases a diagnosis of neoplasm need not be seriously considered. The picture in milder subacute forms may pose considerable diagnostic difficulty with the symptoms, signs, and roentgenographic appearance closely simulating Ewing's sarcoma. In such situations it is imperative that a histologic diagnosis be obtained before instituting treatment. It is particularly inadvisable to commence roentgen therapy before a biopsy (see page 298).

Bone tuberculosis is mentioned by many writers among the possibilities in differential diagnosis but in our experience there have been very few instances where this has been a serious problem. Tuberculosis of bone is usually secondary to joint involvement while neoplasms of bone rarely extend to and invade the articular cartilage.

Luetic infection of bone in children is usually seen in infancy at which time bone sarcoma is decidedly rare. The maternal history and the serology of both the mother and child are ordinarily sufficient to establish or disprove syphilis as the cause of the bone lesion. Roentgenographic findings of bone syphilis may at times closely resemble almost every type of new growth of bone.

Scurvy is seldom seen after infancy. Here, in addition to the bone involvement which is seldom monostotic, there are other clinical evidences of the disease, such as gingival and cutaneous hemorrhages and diminished capillary resistance. In doubtful cases a trial of antiscorbutic therapy will promptly determine the diagnosis. Other juvenile lesions of bone include osteogenesis imperfecta (see p. 677) and chondrodystrophia fetalis.

Hand-Schüller-Christian's disease and eosinophilic granuloma may at times give rise to bone lesions which resemble bone sarcoma of osteolytic type. A biopsy will settle the question and mild roentgen therapy will elicit a favorable response in these granulomatous diseases.

Niemann-Pick's disease, Tay Sachs' disease, and Gaucher's disease may be diagnosed by the presence of characteristic cells in biopsy specimens and their clinical findings are also sufficiently characteristic to prevent their being confused with bone neoplasms.

Trauma to the coverings of bone may at times be succeeded by reparative changes which can resemble early bone sarcoma; we have occasionally seen cases in which there was great divergence of opinion among roentgenologists. In such situations a brief period of delay with serial roentgenograms has enabled us to establish the diagnosis because the similarity of the two conditions rapidly disappears; if it is a neoplasm the succeeding films will show a progressive process while if it is a posttraumatic condition it will either remain stationary or regress.

Children may be subject to skeletal metastasis from adrenal neuroblastoma, retinoblastoma, Hodgkin's disease, lymphosarcoma, and leukemia.

The close similarity of the microscopic picture in Ewing's sarcoma and neuroblastoma is such that pathologists are frequently unable to decide which disease is present in a given case.

A recently described condition known as infantile cortical hyperostoses is discussed on page 698.

PROGNOSIS

Anyone familiar with the outcome of bone sarcoma in children is impressed with the fact that here the prognosis is decidedly more unfavorable than it is in adolescents and young adults. In patients with osteogenic sarcoma or endothelioma under the age of 12 years, survival for periods longer than five years is exceptional. This depressing situation has undoubtedly influenced others—as we must confess it has us—to defer or reject amputation when the ultimate outcome is so uniformly fatal. On the other hand we must admit that amputation is occasionally successful and that no other form of treatment can offer an equal prospect of survival, slight as it admittedly is.

TREATMENT

Conservative measures should be employed in the treatment of benign lesions of bone in children, which are not causing symptoms or threatening the future function of the limb. Bone cyst is fully discussed elsewhere (see p. 122). At the risk of being repetitive it is urged that the use of roentgen therapy of all benign bone lesions in children should be regarded as potentially hazardous and should be reserved for those malignant tumors that are inaccessible to surgical measures. The effect of roentgen therapy on bone growth and the occasional serious late sequelae should serve as a deterrent.

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INTRODUCTION TO SECTION SEVEN

NO ATTEMPT IS MADE TO SET FORTH IN COMPLETE DETAIL THE OPERATIVE technic used in the surgical therapy of bone tumors because such descriptions belong in a textbook of general—or orthopedic—surgery.

In the chapters dealing with osteogenic sarcoma and giant cell tumor allusion has been made to some of the technical features of operations performed for these tumors and applicable to others. Therefore in this part we will consider only those details that are thought to be of value because they apply to the specific surgical problems posed by the nature of the lesions themselves.

48. ANESTHESIA

IN MODERN SURGERY IT IS USUALLY THE CUSTOM TO LEAVE THE SELECTION of the type of anesthesia to the judgment of the anesthesiologist who can best decide which is the safest and most satisfactory method to employ in each individual case. There are no hard and fast rules. The choice may differ depending on the past experience and personal preferences of the one who is to administer the anesthesia. This is a sound principle and holds for operations in the field of bone tumors as well as in other fields.

The physical status of the patient, the site of the operation, the patient's age, the preanesthetic psychic sedation and the depth of the anesthesia all should be considered and regarded as necessary to the individualization of every anesthetic regimen. However, some preferences may be proposed

For aspiration biopsy a local anesthesia is usually sufficient.

For surgical biopsy a short-acting agent, such as cyclopropane, is often ideal.

For curettage of a central bone lesion with filling of the cavity with bone chips or transplants, for removal of an osteochondroma or for minor operations, either pentothal sodium intravenously with nitrous oxide-oxygen inhalation or cyclopropane is suitable.

For major amputations the selection of an agent becomes a matter of utmost importance. This is particularly true of interscapulothoracic, hip-joint, and interilio-abdominal amputations. For the latter procedures, which are usually prolonged and invariably shocking, a general anesthesia is imperative.

Blood loss and surgical shock demand replacement by whole blood which should always be available in the operating room. Also it is well to have an infusion of 5 per cent glucose in saline started prior to the operation.

In the case of shoulder-joint disarticulation or interscapulothoracic amputation where surgical manipulation is of necessity in the vicinity of the patient's upper respiratory airway, intratracheal intubation is of decided advantage. It permits the anesthetic equipment to be arranged more out of the surgeon's field and it also provides a patent airway for the patient at all times.

For bone tumors of the thoracic wall which may necessitate opening the pleura, intratracheal intubation is again recommended in order to control pulmonary ventilation.

Spinal anesthesia, so useful in amputations for other conditions, is not often selected for amputating malignant neoplasms. We prefer the patient to be asleep when the limb is removed. Rarely have we encountered coincident conditions which call for its use. With proper premedication however it is entirely possible to utilize it successfully.

On the other hand, we have no inclination to recommend refrigeration anesthesia chiefly because the conditions for which this technic is so especially suited are almost never found in connection with bone neoplasms.

OUTLINE OF ANESTHETIC METHODS IN OPERATIONS FOR BONE TUMORS

TYPE OF OPERATION	CHILD	ADULT
Aspiration biopsy	Local	Local
Open biopsy	Nitrous oxide-ether	Pentothal-nitrous oxide or cyclopropane
Curettage	Nitrous oxide	Pentothal-nitrous oxide or cyclopropane
Excision		
Minor amputations		
Major amputations	Nitrous oxide	Nitrous oxide-pentothal, cyclopropane, or spinal
Chestwall tumors	Intratracheal ether	Intratracheal cyclopropane
Amputations near upper respiratory tract		

49. CURETTAGE

AMONG THE CONSERVATIVE SURGICAL MEASURES THAT HAVE YIELDED GOOD results in a certain group of localized medullary tumors and allied conditions of bone may be mentioned curettage. Twenty years or more ago the results of this method were often unsatisfactory. This was due partly to the custom then in vogue of packing and draining the wound. Infection, fungation of tumor tissue, and even sepsis were frequent sequelae. With the adoption of primary wound closure far better results were obtained. It is now almost twenty-five years since an amputation has had to be performed at Memorial Hospital because of the unhappy consequences of wound-packing after curettage.

Another reason for some of the earlier operative calamities was the practice of preoperative irradiation. This therapy was found to interfere with normal wound healing by adversely affecting the blood supply and by inhibiting bone repair.

With the abandonment of both of these practices the results of curettage have been definitely improved.

The following conditions are considered suitable for curettage:

- Giant cell tumor in accessible locations
- Solitary bone cyst (unicameral cyst)
- Central chondroma of small bones of hand or foot
- Fibrous dysplasia in localized form
- Nonosteogenic fibroma of bone
- Central lesions in which the diagnosis is uncertain—in preference to removing merely enough tissue for biopsy

TECHNIC OF CURETTAGE (See Figs. 282 and 283)

The skin preparation should be as meticulous as for any open operation on bone. For lesions that are located where a tourniquet can be applied the latter is helpful to the operator since it reduces the blood loss and makes for better visualization of the bone cavity.

The skin incision should be planned so as to afford access to the bone cavity with the least possible damage to overlying soft tissues and especially

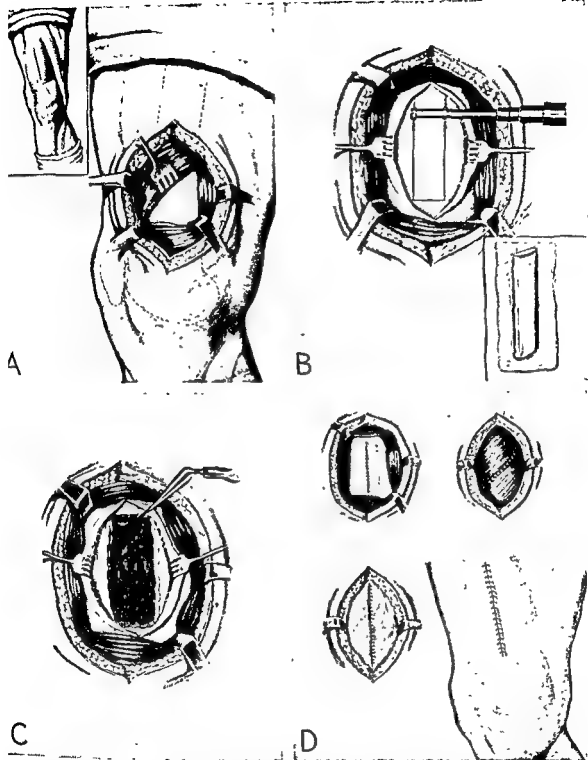


FIG 282. A, Exposure of bone with minimal muscle damage. Inset shows incision over lateral condyle of femur. B, Removal of rectangle of bone to give access to tumor-bearing cavity. Inset shows that the bone removed is kept in saline-soaked gauze and replaced within the cavity following curettage. C, The rectangular window has been enlarged by rongeur and the cavity is being curetted. Note the use of angular curette which permits of thorough removal of tumor tissue from roof of cavity. D, Layer closure of wound. Periosteum, muscle, fascia, and skin all approximated with interrupted non-absorbable sutures.

to important blood vessels and nerves. A thorough familiarity with the anatomy of the region involved is essential.*

When skin bleeders have been tied with fine silk or cotton ligatures



FIG. 262 (Continued). Instruments used in performing a curettage of a central lesion of bone. Note saturated solution of zinc chloride for chemical cauterization of the cavity, which is then thoroughly irrigated with saline, and filled with chips and rectangular bone fragments. The wound is then closed in layers with interrupted sutures, preferably of nonabsorbable material.

towels are immediately fastened to the wound edges to prevent any skin exposure. The overlying fascia is divided and the muscles are either split in the direction of their fibers or, if unavoidable, are cleanly divided with the scalpel. Sufficient exposure simplifies the subsequent steps and facilitates the performance of a thorough operation. The periosteum is incised and reflected over a rectangular area which is then removed with an osteotome or twin-bladed electrically operated motor saw. The window of bone thus removed is placed in sterile saline solution for later use. The opening in the bone thus produced may then be enlarged by rongeur until it is large enough to give access to the entire cavity. The contents are now rapidly removed by curette; during this stage a constant irrigation of the wound combined with suction is decidedly helpful. The use of an angular curette enables the operator to remove the tumor tissue that is attached to the roof of the cavity which cannot be reached by a straight-handled curette. The entire cavity should be cleared of all soft tissue until healthy bone is reached. When the field has been sucked or sponged dry a thorough swabbing of the interior of the bone with a saturated solution of zinc chloride

* Two useful works are: NICOLA, T. *Atlas of Surgical Approaches to Bones and Joints*. New York, Macmillan, 1945. HENRY, A. K. *Extensile Exposure Allied to Limb Surgery*. Baltimore, Williams & Wilkins, 1945.

is followed by a vigorous flushing of the cavity with normal saline solution which is removed by continuous suction. Zinc chloride should not be permitted to come in contact with any other part of the wound. The latter is closed in layers with interrupted sutures of cotton or silk, great care being exercised in the coaptation of muscles and fascia and in accurate skin approximation (see Fig. 282 for instruments used in performing curettage).

The cavity is usually filled with bone chips taken from the iliac crest or strips of cortical bone taken from the tibia by means of the motor saw. These rectangular bone segments are placed in the cavity with their long axis corresponding to that of the recipient bone (see Fig. 283, page 490). In most instances we prefer cancellous to cortical bone.

The more extensive the cavity and the older the patient, the greater is the need for introducing bone to bring about regeneration of osseous tissue and complete filling in of the defect.

Dressings should be bulky and applied with firm pressure. Splints or casts are used if the situation seems to indicate them in order to prevent a pathologic fracture. Whenever possible they should be avoided and the early return of muscle- and joint-function should be encouraged.

USE OF HOMOGENOUS BONE GRAFTS

While our experience with bone chips or larger grafts has until recently been confined almost entirely to autogenous material the recent experience of Wilson and of Bush at two orthopedic clinics supports the belief that homogenous grafts have a definite place in bone surgery and that a bone bank can serve as a useful source from which the needed material may be obtained at all times. Blood type and Rh factor do not appear to influence the results. Bush reports that at the New York Orthopedic Hospital such homogenous grafts were used in 67 operations with but four complications. For filling bone defects after curettage of cysts, giant cell tumors and other similar lesions, as well as in other situations requiring bone transplants, it seems certain that bank bone will serve a useful purpose.

Experiments by Kiehn, Friedell, and MacIntyre, the results of which have not yet been published, indicate that in animals, refrigerated bone remains dormant for about four weeks after transplantation. Their conclusions were arrived at with the help of tracer doses of radioactive isotopes. After four weeks the refrigerated bone exceeds the capacity for assimilation and approximates that of unrefrigerated vital grafts.

During the past year we have used bank bone rather extensively and with satisfactory results.

50. RESECTION

ANOTHER CONSERVATIVE MEASURE WHICH IS ADAPTABLE FOR BONE TUMORS is that of resection (partial excision) of the tumor-bearing area. In favorable situations it may be a justifiable substitute for amputation, especially in the following conditions:

Benign cartilaginous tumors, e.g., osteochondromas

Giant cell tumors of the proximal end of the fibula and distal end of the radius

Tumors of the scapula, clavicle, sternum, and rib

Selected cases of low-grade fibrosarcoma of bone affecting the ulna or fibula (see Figs. 284-286)

Rarely for a low-grade chondrosarcoma of a major bone, such as the humerus or femur

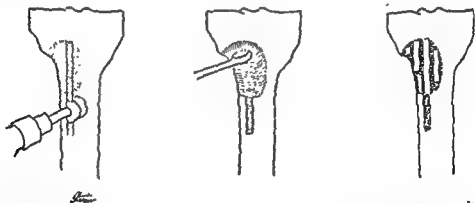


FIG 283. One method of obtaining cortical bone fragments to fill defect resulting from curettage of a low-grade chondromyxosarcoma (See Fig. 152, p 233).*

The resection should also aim to remove not only the tumor-bearing area but a sufficient margin of adjacent normal bone. It is unsafe merely to chisel away the prominent portion of the tumor while leaving part of it attached at its base to the bone from which it arises (see Fig. 287 A). We have found it convenient in those cases in which a large protuberant mass is attached by a relatively narrow stalk to chisel through the narrow portion and remove the neck of the tumor in a single piece; this then permits an

* Figure 283 is discussed on page 489.

easy excision of a segment of normal bone including the stem or stalk and assures the operator that the removal is complete.

Total excision is applicable to clavicular and scapular tumors. Segmental



FIG. 284. *Left*, central chondromyxosarcoma of proximal end of humerus; *right*, gross specimen.

resection has its field of usefulness in lowgrade tumors of the humerus and femur and, under some circumstances, in other long bones (see Fig. 288). The removal of a segment of the shaft of a long bone requires that a bone graft be used to substitute for the part excised (see Figs. 64, p. 145, and Fig. 284).

TECHNIC

The skin is excised over the affected area and the incision is deepened to expose the bone. The periosteum is split and reflected and the desired portion of bone is removed by an osteotome, chisel, or bonecutter. In removing pedunculated or projecting tumors it is important that the base be saucerized in such a manner as to insure the extirpation of all abnormal tissue.

For example, resection of a part of the fibula requires a long incision and dissection of the muscular attachments so as to skeletonize the portion that is to be removed. Division of bone by either a Gigli saw or bonecutter



FIG. 284 (Continued). Appearance following segmental resection. The resected portion of bone is replaced by the proximal end of the fibula.

is then easily accomplished. Care should be exercised in dealing with osteochondromas of the upper humerus and upper fibula not to injure the musculospiral nerve and the peroneal nerve; this is not an easy matter when the tumor in the upper fibula is bulky.

Total excision of the clavicle requires considerable dissection and avoidance of injury to a number of important structures. Excision of the entire clavicle is performed through a horizontal incision which extends from the acromial to the sternal end directly over the bone. Division of the acromioclavicular ligaments and disarticulation at the acromioclavicular joints permits the clavicle to be raised anteriorly and the muscles of attachment to

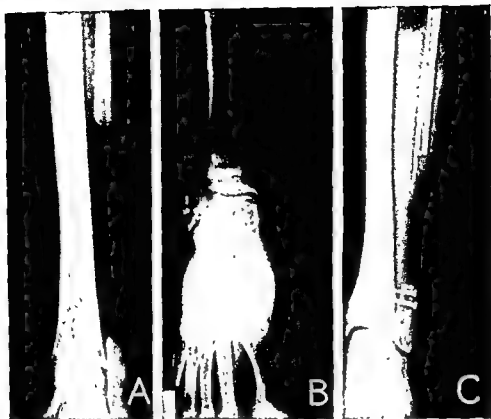


FIG. 285. Three different methods of stabilizing ankle after resection of lower fibula for endothelioma. A, Bone peg; B, bone transplant; C, vitallium screws.

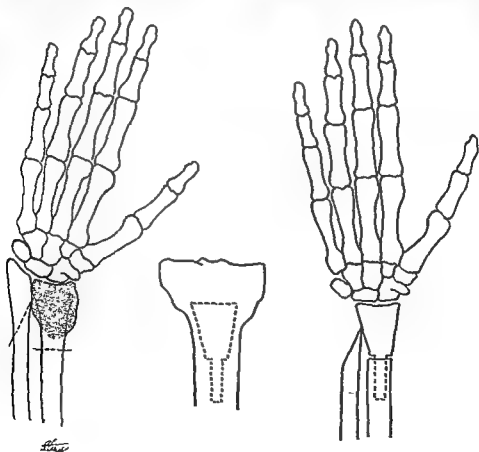


FIG 286. Resection of benign tumor of radius, e.g., giant cell tumor, and substitution of tibial transplant—after Colonna.



FIG. 287. Method of resecting localized bone tumor. A, Incorrect; B, correct, C, final appearance.

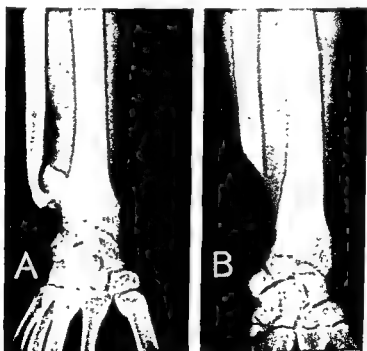


FIG. 288 A, Osteochondroma of lower radius, B, appearance after resection of tumor and distal portion of ulna. (William Beaumont General Hospital.)

from benign chondroma to malignant chondrosarcoma is often insidious it should be emphasized that partial excision is not without danger (see Fig. 157, p. 286).

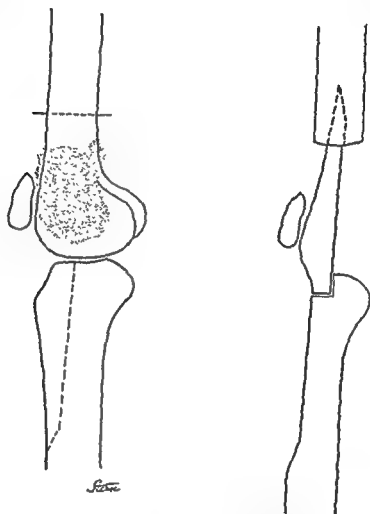


FIG. 290. Illustrating Colonna's method of resecting borderline tumors of lower femur as a substitute for amputation.

Frankly malignant tumors of the scapula may also deserve consideration of the more conservative procedure of total scapulectomy as an alternative to interscapulothoracic disarticulation. If the operator believes that he can successfully remove all of the primary tumor he is justified in the attempt to save the arm. And if following scapulectomy there is no recurrence in or about the operative area even if distant metastases develop, he can be confident that his conservatism was wholly justified.

TECHNIC

The incision will vary somewhat according to the size of the tumor and the portion of the scapula chiefly affected. In general an inverted L-shaped incision gives satisfactory exposure. The vertical line passes upward 2 cm. lateral to the vertebral border of the scapula to a point slightly above the base of the spine where it turns horizontally to extend laterally to a point

opposite the acromial tip. The resulting triangular flap is raised exposing the major part of the posterior surface of the bone. Division of the muscles attached to the vertebral border and inferior angle permits elevation of the

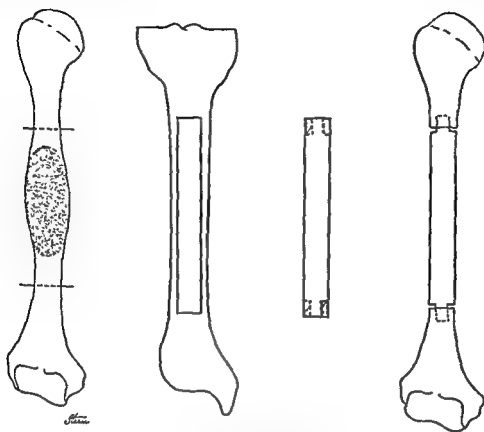


FIG. 291. Schematic drawings illustrating steps in segmental resection with substitution of a massive tibial transplant.

bone sufficiently to enable the operator to divide the subscapularis muscle. The supra- and infraspinatus muscles are cut near their humeral attachments, the shoulder joint is opened, coraco-acromial ligaments are now divided, and the entire scapula with attached muscles is removed. Preservation of as much of the deltoid as possible assists in maintaining the position of the humerus in close apposition to the outer end of the clavicle. The wound is then closed in layers without drainage, the arm being immobilized in a Velpeau bandage or a sling.

Early hand and elbow movements are encouraged. The degree of shoulder-girdle function that is attained is surprising (see Figs. 162, p. 289; 170, p. 296; and 289).

Phemister and others have demonstrated that resection can be successfully employed for segmental removal of a long bone such as the femur. We have used it on four occasions for lesions occurring in the middle third of the humerus. The resected segment is replaced by a massive tibial transplant which under favorable circumstances unites firmly at both ends

and subsequently attains much of the shape and appearance of the rest of the bone into which it has been placed. One may replace extensive areas of the humerus or ulna, for example, by massive tibial transplants which



FIG. 292. Vitallium prosthesis used to replace upper portion of femur. (Courtesy of Austenal Laboratories, New York.)

are doweled so as to fit snugly into the remaining shaft (see Figs. 290 and 291). The dowel may be secured further by a transfixion screw but this is not essential.

When resecting a rib tumor it is sufficient to remove a segment of only the affected rib if the lesion is benign; when the tumor is malignant we prefer to resect the rib above and below the one involved.

In a consideration of conservative measures one should include a reference to the use of Vitallium or plastic cups or other types of substitutes for joints which permit of resection of the diseased segment of bone in lieu of amputation.

Moore's classical case of resection of the proximal part of the femur with utilization of the metal appliance pictured in Figure 292 is a good example.

We recently saw Wilson resect a giant cell tumor of the head and neck of the femur and place a Vitallium cup much as is done in an ordinary arthroplasty. Such procedures have their place and their use will unquestionably be increased as more experience is accumulated (see Fig. 293). However, the selection of cases for operations of this type requires a great

deal of thought and the exercise of good judgment particularly for lesions which are not entirely benign. This is true because if an operation of this sort is selected in lieu of an amputation and a local recurrence takes place

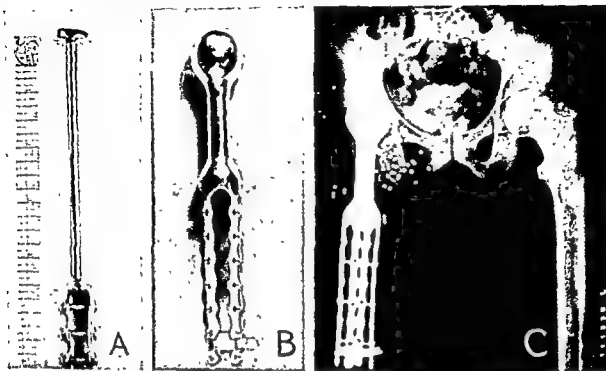


FIG. 293. A, Prosthesis used to replace proximal portion of radius. B, A simpler type of prosthesis for upper femur (courtesy of Austenal Laboratories, New York). C, Roentgenogram of case in which bone loss was due to gunshot wound (courtesy of Dr. Lyon K. Loomis, New Orleans, La.).

the chance of saving the life of the patient by a second operation (i.e., amputation) is definitely lessened.

51. AMPUTATION

PSYCHOLOGIC CONSIDERATIONS OF A MAJOR AMPUTATION FOR MALIGNANT DISEASE

SINCE IN AMPUTATION THE PATIENT IS OFTEN A CHILD OR AN ADOLESCENT the shock of being disfigured and disabled permanently with the resulting curtailment of activities is more severe than it would be for an older person. The parents of young girls often find the thought of a change in their daughter's future life so depressing that they refuse to give their consent to the amputation even though it has been explained to them that this measure offers the only hope of survival.

Having obtained permission in writing from both parents it is well to plan for the operation without disclosing its nature to the child until the day preceding the operation. Then after patiently explaining the circumstances and the decision to amputate it is well to administer a sedative in order to help combat the excitement and psychic shock. It has not seemed justifiable to perform an amputation on a child without his knowledge as the shock later is apt to be serious.

Avertin as a basal anesthesia, or premedication with barbiturates, is then utilized to bring the patient to the operating room in as calm a state as possible. The surgeon can never be too busy to explain the whole situation in detail to the parents and later to the patient. If he leaves this unpleasant task to someone else he is evading a vital responsibility. When he himself explains the situation he will generally find that his decision is accepted by the family and the patient. In the case of the latter the immediate psychologic explosion is usually less severe and of shorter duration than it is for the parents.

Later mental disturbances have, in our experience, been exceedingly infrequent. If the malignant disease remains cured or under control the patient proceeds to adapt himself to new conditions.

With the steady improvement that is being made in prosthetic appliances the ability of the amputee to get about, to earn a living, and to enjoy a contented, worthwhile life is being correspondingly enhanced. We have had a number of girls, who, following amputation, later married, had children.

and led happy and useful lives. In not one instance has any of our patients who recovered from an operation and from the disease which necessitated it ever given the slightest indication that he regretted the decision.

The medical attendant derives a certain measure of comfort from the thought that the patient would certainly succumb to the disease were an amputation not performed. This knowledge entails upon him a moral responsibility to exert every persuasive power at his command to gain the consent of the patient, or of the parents if the latter is a minor, to have the amputation performed.

PREOPERATIVE PREPARATION

Before amputating a limb for malignant bone tumor the following steps should be observed:

1. The diagnosis should be established beyond reasonable doubt. In this connection the histologic evidence is the least subject to error; the clinical and roentgenographic evidence is also extremely important.
2. A roentgenogram of the lungs should be taken.
3. Blood should be on hand for possible transfusions during or immediately following the operation.
4. A careful, preferably forty-eight-hour, skin preparation should be carried out and the parts covered with sterile dressing.

TECHNIC OF AMPUTATION

Blood loss should be reduced to an absolute minimum. A tourniquet is advisable. The newer pneumatic types are satisfactory but are *not* essential. Experience in the application of the rubber tubing tourniquet can be acquired readily and, if used with Wyeth pins for high thigh or upper arm amputations, will not slip when the muscles retract after division and before ligation of the main blood vessels can be accomplished. For interscapulothoracic amputations, however, a tourniquet cannot be used, and it is best to secure the subclavian vessels first. This is accomplished by resecting several inches of the clavicle (see Fig. 298, p. 514).

INCISION FLAPS

In the upper extremity the incision is a modified circular one with flaps of about equal length. In the lower extremity, long anterior and short posterior flaps are best but the location of the tumor may necessitate atypical flaps. If the skin flaps are too short, undue tension will result when they are closed. If they are too long, they can be readily tailored for a snug fit.

LEVEL OF AMPUTATION

The importance of the level of the proposed amputation cannot be over-emphasized. As has already been referred to (see p. 255), there is con-

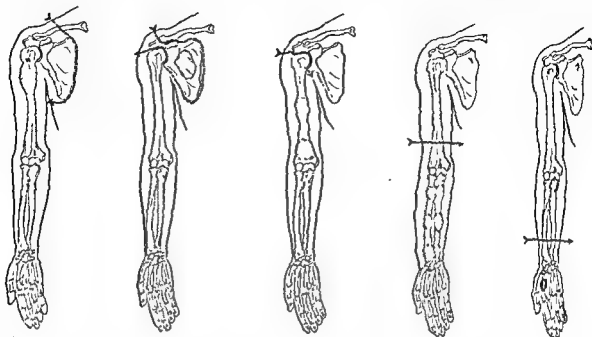


FIG. 294. Proposed levels of amputation for malignant tumors of the upper extremity.

vincing evidence that the traditional concept that amputation for sarcoma should under no circumstances be performed through the bone in which the sarcoma originated is not justified by the facts. While we have been satisfied that osteogenic sarcoma of the lower femur may be safely subjected to a high thigh amputation we have usually followed this dictum in cases arising in the lower ends of other long bones. For one thing, the incidence of this tumor in the ankle or elbow region or wrist is low and cases where a decision has to be made are not often seen. We venture the opinion, however, that the same principles apply here as to cases of lower femur sarcoma and suggest that if the same care is exercised in the selection of the level for each individual case as is used in the cases of sarcoma of the lower femur, the safety of the more conservative procedure will be demonstrated. For the proposed levels of amputation see Figures 294 and 295.

TYPES OF AMPUTATION

For the lower leg and forearm the classical time-honored procedures in common use are quite satisfactory. For supracondylar amputations applicable to tumors of the upper tibia the Callander procedure is considered excellent. Disarticulation at the shoulder joint gives a better cosmetic result than interscapulothoracic disarticulation but for the upper humerus the latter procedure is usually safer.

DIVISION OF BONE

The bone is divided transversely with a saw and at a level one-eighth of an inch below the circular division of the periosteum. This level is de-

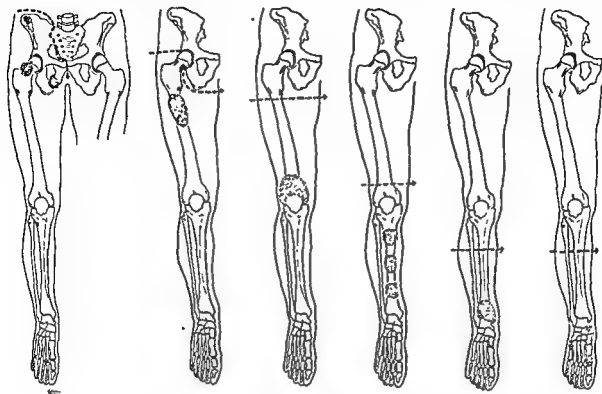


FIG. 295. Proposed levels of amputation for malignant tumors of the lower extremity.

termined by the operator at the time the skin incision is planned and is high enough to permit the soft parts to cover the bone end snugly but, without undue tension. The edges are gently smoothed with rongeur and file but the marrow is left undisturbed; it is never curetted.

DISPOSITION OF BLOOD VESSELS AND NERVE TRUNKS

The main arteries and veins are now carefully isolated and doubly ligated with heavy silk or cotton ligatures. The nerve trunks are isolated and dissected proximally to permit of high ligation with the same ligature material, after which 1 per cent Procaine followed immediately by 95 per cent alcohol is injected slowly with a fine gauge needle, so as to swell the nerve trunk above the ligature. The part of the nerve below the ligature is then excised. It is believed that traction on nerve trunks to permit of severance at a higher level is apt to result in painful neuritis and causalgia. In order to secure a high division of the nerve trunk it should be gently dissected proximally without traction and then ligated, injected, and severed. By this means the development of terminal neuromas is avoided and late causalgias seldom result. Having dealt with the bone end, the tourniquet is loosened and all bleeding points clamped and ligated.

WOUND CLOSURE

The question of the advisability of completely closing an amputation stump without provision for drainage has been a troublesome one. Ideally we should be able to obtain perfect healing of the wound with no drain used at all. In many cases we have attained this ideal. However, in a considerable number of cases, despite every precaution, collection of blood or serum has formed beneath the flaps and required aspiration or occasionally evacuation through the wound itself. This has forced us reluctantly to advise that thin strips of rubber dam be placed at the angles of the wound. These are removed on the third day and the places where the drains emerged are then closed by tying sutures that were left untied at the time of the operation.

COMPLICATIONS OF SURGICAL TREATMENT

Among the complications that may follow an amputation for malignant bone tumor are: shock, hemorrhage (immediate or secondary), infection, hematoma, and wound dehiscence.

Shock can be minimized by speed, gentle handling of the tissues, and prevention of blood loss; the latter may be combated by use of plasma and whole blood transfusions.

For postoperative hemorrhage the treatment should be preventive, that is, great care should be exercised in the application of ligatures to all bleeding vessels, with double ligation of the large vessels, and avoidance of infection which is an important factor in secondary hemorrhage. A tourniquet should be fastened in plain sight to the head of the amputee's bed and not removed until the wound has firmly healed. Should a hemorrhage occur, the usual supportive measures are indicated after stopping the hemorrhage by pressure, packing with gauze, or even exposure and ligation (under tourniquet) if the bleeding vessel is large.

Hematoma is prevented by: (1) meticulous hemostasis, (2) snugly applied, well-padded dressings, and (3) where necessary, drains to prevent the accumulation of fluids beneath skin flaps.

Wound dehiscence may be due to too early removal of sutures but can usually be attributed to suture of edges under excessive tension (i.e., flaps that are too short), retarded wound-healing resulting from the effect of previous radiation on the tissues, or separation of flaps because of hematoma or infection.

INTERINNOMINO-ABDOMINAL AMPUTATION

More than fifty years have elapsed since this most shocking and mutilating of all amputations was first performed by Billroth in 1891. Four years later Girard completed the first successful operation. During the next

forty years less than half the patients survived. However, in 1935 Gordon-Taylor revived interest in the procedure; he reported 5 personal cases and gave an account of his technic. In 1940 he added 6 more personal cases with a mortality of 33 per cent. Sugarbaker and Ackerman, in 1945, collected records of 132 cases including 6 of their own; in the latter the mortality was 33 per cent. Pack and Ehrlich, in 1946, reported 6 additional cases from Memorial Hospital with no operative mortality.

Sugarbaker points out that while the mortality for all reported cases is 28 per cent it has fallen from 56 per cent in the past ten years. The credit for this improvement is doubtless due partly to the improved preoperative management but chiefly to the more efficient handling of shock which is the major hazard.

INDICATIONS

The necessity for this grave and mutilating operation is rarely encountered. Bone tumors of the innominate bone or upper femur, soft-tissue sarcoma about the hip too extensive for excision (neurogenic sarcoma, myosarcoma), and, in exceptional cases, osteomyelitis of pelvic bone (Morton) may be suitable for this procedure.

PREOPERATIVE MANAGEMENT

Since shock and hemorrhage are the principal causes of fatality it is essential that they be combated as fully as possible. This involves the use of large amounts of whole blood, of which at least 2 liters ought to be on hand in the operating room. If the patient is anemic, transfusions prior to the operation are advisable. In the female it is considered a wise precaution to render the perineal and operative fields as clean as possible by preoperative cleansing douches. Before the patient is taken to the operating room an urethral catheter, preferably of the Foley type, is inserted.

ANESTHESIA

The patient ought to be asleep; therefore, if a continuous spinal is chosen, enough intravenous sodium pentothal should be administered to keep him unconscious. If inhalation anesthesia is selected, nitrous oxide-ether or cyclopropane is satisfactory. Due to the effect that it has on blood pressure, continuous spinal anesthesia is not considered the method of choice although Sugarbaker employed it in his cases.

OPERATIVE TECHNIC

The patient is placed on the table with a sand bag under the sacrum in such a way as to tilt the entire pelvis toward the unaffected side. By this means the anterior and posterior flaps can be outlined without disturbing the patient's position. In the male the genitals can be kept out of the field by a temporary suture placed in the scrotum and attached to the op-

posite thigh. The operation generally selected by surgeons in recent times follows closely the principles enunciated by the English surgeon, Hogarth Pringle, in 1916. The incision commences at the anterior-superior spine and follows the general direction of Poupart's ligament to end at the symphysis pubis. It is extended posteriorly along the crest of the ilium, dipping down to course above the greater trochanter and follows along the gluteal groove to the perineum from which it extends forward to meet the medial end of the anterior incision just above the symphysis pubis. The inguinal ligament is divided at its lateral and medial attachments to the anterior-superior iliac spine and pubis respectively. In the male the spermatic cord is preserved and retracted medially. The peritoneum is stripped upwards and medially with the abdominal contents and held in position with a laparotomy pad. The bladder is reflected downward and medially, exposing the iliac fossa with its contents. The ureter must be identified, and the rectum and bladder are the other organs that must constantly be kept out of harm's way. The external iliac artery is ligated doubly and divided, and the limb elevated for one or two minutes before clamping, ligating, and dividing the external iliac vein. The common iliac artery is identified above the bifurcation of the external and internal branches and a special, rubber-covered clamp is placed on the internal iliac artery for temporary occlusion (see Fig. 296). The pubic symphysis is then denuded of soft-part coverings—which include the insertion of the rectus abdominis muscle—and divided with a Gigli saw or chisel. Hemorrhage from the ischiocavernosus in the male or from the constrictor vaginae in the female may be troublesome but can be controlled by prompt packing.

The posterior skin flap is now reflected back as far as the sacrum. The crest of the ilium is exposed by dividing the quadratus lumborum and other muscles that attach to the crest. The iliopsoas muscle is cut as high as possible together with the iliacus, pyramidalis, gemelli, and levator ani muscles. The sacroiliac joint is now exposed and disarticulated, using a chisel. As Pack and Ehrlich point out, the bevel of the chisel should be directed away from the midline; also care should be exercised not to injure the hypogastric vein. Bleeding at this point may be troublesome and should be controlled by packing. The gluteal muscles are then divided, followed by cutting of the major ligaments of the sacrum. This leaves the specimen attached principally by the great nerve trunks. These are injected with novocaine followed by alcohol and ligated. The specimen is removed. It is surprising how much smaller the wound appears than was anticipated during the operation. Excessive skin and loose muscle tags are removed and the flaps are approximated with interrupted sutures leaving two cigarette drains to emerge at either end of the wound. Skin approximation should be meticulous. A large, well-placed, bulky, gauze dressing is applied with even pressure.

During the operation blood is constantly running into the arm of the

unaffected side and at critical periods in the procedure when blood pressure falls, e.g., when the sacroiliac joint is divided, the use of a vein in the foot on the contralateral side for simultaneous inflow of blood is of decided advantage. It is necessary to use relatively large amounts of blood and plasma during the course of the operation, e.g., in a recent case 2 liters of whole blood and 1 liter of plasma were administered during the three hours required to complete the operation. By this means the patient was returned from the operating room with a blood pressure somewhat higher than it was when the anesthesia was commenced.

POSTOPERATIVE MANAGEMENT

Shortly after the patient has become fully conscious a Wangenstein suction apparatus is installed connected with a Levine tube passed through the nostril. This is used during the first forty-eight hours to prevent distention; at the end of this time, when gas begins to pass, the tube can be removed and the patient can take a soft diet. Tidal drainage is connected with a Foley catheter; this prevents bladder distention during the period of several days before bladder tone is recovered and normal urination takes place. Additional supportive therapy by means of blood and plasma transfusions is given as indicated. These cases require careful observation to insure that their electrolyte and plasma protein balance is well maintained. Large doses of vitamins are given in the infusions.

Those who favor early ambulation will find that in some instances these patients may be allowed up in a chair on the second postoperative day; whenever this is possible we consider it advisable. However the general condition of the patient and the promptness with which he recovers from the operation must be considered.

Penicillin begun prior to the operation is continued in amounts of 100,000 units every eight hours until the danger of serious wound infection is passed. Since the location of the incision favors contamination with organisms of the *E. coli* group, which are not susceptible to penicillin therapy, it has seemed to us advisable to supplement the latter drug with streptomycin. Owing to the size and extent of the incision and the numerous opportunities for pocketing of infection, any combination of methods of preventing this unfortunate postoperative complication ought to be taken. Unlike amputations in other locations it seems inadvisable to remove the drains as early as the second day, for the profuse drainage—which continues for many days—must be allowed egress.

HIP JOINT DISARTICULATION

INDICATIONS

In the past disarticulation at the hip was regarded as the operation of choice for sarcoma of any portion of the femur. However experience over

a period of many years has convinced us that for the majority of osteogenic sarcomas and chondrosarcomas arising in the lower fourth of the femur amputation at this level is neither necessary nor advisable (see p. 256). The operation should be reserved for osteogenic sarcomas and chondrosarcomas situated in the middle or upper thirds of the bone where clinical and roentgenographic examination indicates that the entire diseased area can be removed. On the other hand Ewing's sarcoma of the femur at any level—which tumor has a tendency to extend much more widely than can be determined by either physical or roentgenographic examination—should have amputation at the hip.

The infrequency with which this level has been chosen for cases operated upon in the Bone Tumor Service of Memorial Hospital shows that it is not often indicated. During the period from 1930 to 1946 the operation was performed 15 times.

TECHNIC OF OPERATION

The patient is placed on the table so that the affected thigh is abducted and rotated externally. A "short-handled" racquet incision is made with the longitudinal portion commencing just above the midpoint of Poupart's ligament and coursing downward along the femoral vessels for a distance of from 4 to 6 cm. The vessels themselves are at once identified and the artery is immediately divided between ligatures, being certain that this is done proximal to the origin of the profunda artery. The limb is elevated for several minutes in order to drain the venous blood prior to doubly ligating and dividing the vein. The circular portion of the incision now commences at the lower end of the vertical part, continues downward and medially below the groin, passes posteriorly and curves across the lateral aspect above the base of the greater trochanter to meet the anterior incision.

The skin, subcutaneous tissues, and deep fascia are now reflected to form flaps. The muscles are divided in groups as follows: anteriorly, the sartorius, tensor fasciae femoris, rectus femoris, and psoas; medially, the adductors which are divided below their pubic attachments; laterally, the obturator, gemelli, pyriformis, and gluteus medius. The joint capsule is now opened widely, the head luxated out of the socket and freed by dividing the ligamentum teres. The hamstring muscles are now cut and the sciatic nerve injected with novocain in 1 per cent solution and subsequently with 95 per cent alcohol following division and ligation.

Hemostasis having been accurately secured, wound closure is effected by means of interrupted sutures of muscles and subcutaneous layers and skin. Nonabsorbable suture material is preferred. An effort should be made to secure adequate soft-part cushioning of the ischial tuberosity since if a prosthesis is to be attempted weight will be borne at this point against the "tilt-table" of the artificial limb.

Drainage, always to be avoided wherever possible, is generally desirable

in an amputation at hip level because of the inevitable serosanguinous accumulation which, if not allowed to escape, may prevent firm and uncomplicated wound healing. Drains of rubber dam should be small and thin and removed within seventy-two hours. If sutures are placed at the site of the drains and tied when the latter are withdrawn, primary wound-healing is likely to occur.

Care must be taken to apply a voluminous dressing under even pressure. For this purpose elastoplast has proved more satisfactory than ordinary adhesive plaster.

POSTOPERATIVE MANAGEMENT

Bladder distention should be prevented by the introduction of a Foley catheter at the first indication that the patient is not properly emptying the bladder. Blood loss must of course be made up by transfusion. Shock is not a common complication although it is present to a certain extent in all cases of hip-joint disarticulation. A rapid pulse may persist for a few days, especially in children or young adults, but this of itself requires no treatment. Other complications, such as severe anemia, tympanites and urinary retention, wound infection, postoperative phlebothrombosis, and pulmonary infarction are not often encountered. Convalescence is usually surprisingly smooth. Penicillin and streptomycin are useful in preventing infection in a wound that of necessity passes near the anus and is subject, at least theoretically, to the danger of contamination with organisms of the colon group. Early shortening and removal of drains is essential; they can favor infection if left too long in situ.

HIGH-THIGH AMPUTATION

This is the level at which the majority of amputations for bone neoplasms are performed since the distal portion of the femur is the site at which osteogenic sarcoma and chondrosarcoma are most frequently found. The level at which the femur is to be divided having been determined, Wyeth pins are inserted and after elevation of the limb a tourniquet of heavy rubber tubing is applied and fastened (see Fig. 297). Flaps of skin and fascia are outlined after the modified circular incision has been made. Generally these flaps are anterior and posterior of nearly equal length. It requires practice to so fashion them that closure will provide a covering that is neither redundant nor tense. When the flaps have been reflected to the desired level the muscles are divided rapidly down to the bone and dissected proximal to the point where the latter is to be divided. The periosteum is then cut and reflected distally and the femur is sawed through one-quarter of an inch distal to the periosteal line. The femoral artery and vein are ligated, the sciatic and femoral nerve trunks are injected after liga-

tion, and any other visible arteries and veins clamped and tied before loosening the tourniquet. Thereafter all bleeding points are caught and tied and the wound is closed with interrupted silk or cotton sutures, making

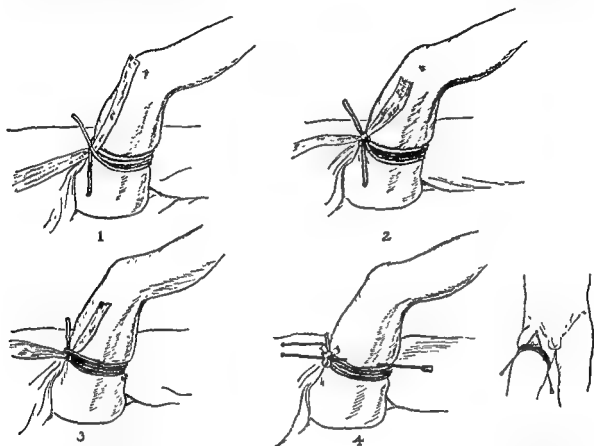


FIG. 297. Technic of applying Wyeth pins and tourniquet for amputation of thigh. 1, Tourniquet applied about thigh, several coils; ends crossed over a double fold of two-inch muslin bandage. 2, Half knot tied in the bandage. 3, Tubes crossed in reverse direction. 4, Double knot (square) tied in bandage. *Note:* In 1, 2, and 3 the artist has omitted the Wyeth pins for the sake of clarity but the pins should be inserted before the tourniquet is placed about the limb and fastened according to the technic described.

no effort to bring the muscles over the bone end but relying on fascial approximation followed by that of skin and subcutaneous tissue. Drainage may be instituted or omitted according to the preference of the surgeon. If drains are not used accumulations of blood and serum may require subsequent evacuation by aspiration. The meticulous application of even pressure may prevent such accumulations but they will sometimes occur despite this precaution. If drains are used they should not be left in place for more than seventy-two hours.

The postoperative care is usually a simple matter. Patients are allowed up in a chair on the first postoperative day and are given crutches soon thereafter.

AMPUTATION ABOVE THE KNEE

INDICATIONS

Malignant tumors of the upper fibula or tibia, with exceptions, require amputation above the knee. For this purpose it is entirely practical, in most instances, to preserve the long stump of the femur made available by a supracondylar level, such as is possible with the Callander amputation. Since this procedure is described more or less in detail in surgical textbooks it is unnecessary to repeat it here.

For bulky tumors of the proximal ends of the leg bones a slightly higher level of amputation may be desirable. In such instances long anterior and short posterior flaps or modified circular incisions are suitable. Tourniquet and Wyeth pins are used and the technic does not differ materially from that described for high thigh amputation.

While the Gritti-Stokes operation may have its place it is rarely selected in our clinic.

AMPUTATION BELOW THE KNEE

This level of amputation is seldom required. It should be reserved for the rare malignant tumors of the tarsal and metatarsal bones and for a selected few occurring in the lower portion of the tibia and fibula.

TECHNIC OF OPERATION

The site of election, if possible to select it, should be in the middle third of the leg with a 16 to 18 cm. stump measured from the joint line of the knee. If performed at a lower level the circulation of the stump is often poor; if at a higher level than 8 cm. below the joint, unsatisfactory leverage results in functional impairment.

The fibula is frequently a source of annoyance and is responsible for many of the reamputations required for painful or ulcerating stumps. If it is transected two or more inches higher than the tibia these sequelae may generally be avoided.

The operation is more readily performed with the patient lying in a prone rather than a supine position. The incision is made so as to provide a long posterior and short anterior flap; the former includes the aponeurotic tendon of the gastrocnemius. In no other amputation is it easier to misjudge the flap length. If cut too sparingly the sutures are under tension and ulceration by pressure of the anterior corner of the tibial stump may result or the patient will hold the knee flexed postoperatively and a contracture may readily take place. Redundant skin is also undesirable. Perfect tailoring of flaps that are cut generously at the outset will secure satisfactory stump ends. Drains may usually be dispensed with; if used they should

be removed within forty-eight hours and the gaps in the skin closure approximated by tying sutures placed but left loose at the time of operation.

AMPUTATIONS OF UPPER EXTREMITY

GENERAL CONSIDERATIONS

While it is considered advisable to perform amputations of the extremities for malignant tumors with the primary objective of removing a sufficient amount of the limb to insure against local recurrence one ought to conserve as much of it as is consistent with safety.

For tumors of the scapula not suitable for total scapulectomy, and of the upper humerus, an interscapulothoracic amputation is indicated.

For those rare tumors situated in the lower end of the humerus the decision rests between a level in the upper part of the arm and a shoulder joint disarticulation. The latter is preferred because of the additional safety factor with little added impairment of function. However each case must be considered individually. When in doubt the higher level should be selected.

For suggested levels of amputation for tumors in bones of the upper extremity the reader is referred to Figure 294, p. 502.

INTERSCAPULOTHORACIC AMPUTATION

Indications

The operation of choice for malignant tumors of the upper humerus and shoulder joint region, including those arising in the glenoid or neck of the scapula, is interscapulothoracic amputation (see Fig. 298). Not only for cases in which an ultimate cure is a possibility but for incurable cases with pulmonary metastases it is a justifiable procedure. It is indicated for malignant tumors of the clavicle and scapula only when the growth encroaches on the shoulder joint and renders impossible total excision of these bones.

Technic of Operation

For the *Berger Operation* the patient is placed on his back with the involved shoulder elevated to permit skin preparation well beyond the midline both front and back. The arm is well wrapped in sterile sheets from fingers to shoulder and left free to be held by an assistant who may change its position to facilitate the anterior or posterior dissection of the shoulder.

A linear incision made over the middle third of the clavicle is extended through the soft tissues to the periosteum. A 5 or 6 cm. segment of the clavicle is now resected, preferably with a Gigli saw. This gives access to the subclavian vessels. The artery is more deeply situated beneath the vein. The cords of the brachial plexus are seen above the vessels. The sub-

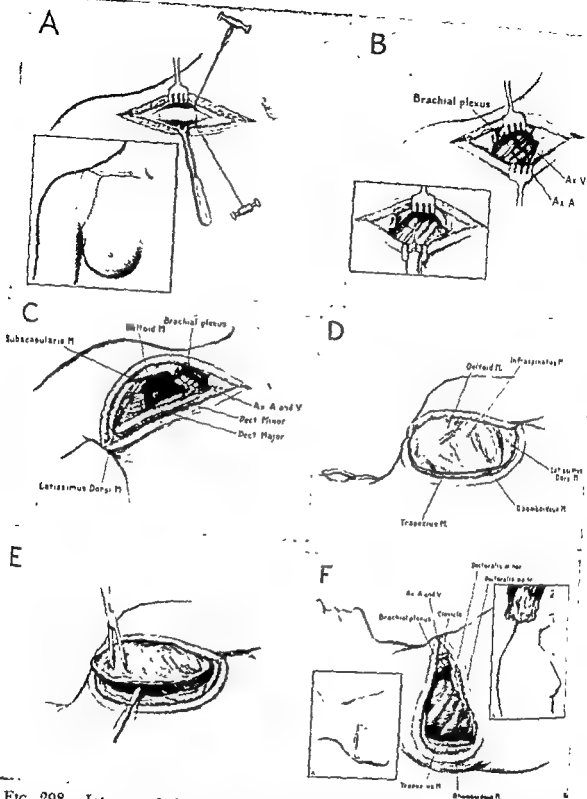


FIG. 298. Interscapulothoracic amputation. A, Incision for preliminary division of clavicle for ligation of axillary vessels and brachial plexus. B, Double ligatures placed on axillary artery and vein and single ligature on nerves. Inset shows injection of nerves above ligature with 95 per cent alcohol. C, Division of nerves and vessels, pectoral muscles, and latissimus dorsi muscles. D, Incision carried posteriorly shows muscles attached to scapula. E, Volsellum grasping scapula near the vertebral border. Scalpel dividing muscles along vertebral border and beneath it (subscapularis muscle). F, Wound ready for closure. Insets demonstrate transverse linear scar. (From Pack, G. T. and Livingston, E. M.: *Treatment of Cancer and Allied Diseases*. New York, Hoeber, 1940.)

clavian vein and artery are freed separately by careful dissection and, using a ligature carrier, each is surrounded by three separate ligatures. Two are tied proximal to the intended point of division and one distal thereto. The vessels are then divided and the nerve trunks also ligated, divided, and the proximal ends injected with novocain followed by 95 per cent alcohol.

The skin incision is then extended to the tip of the acromion and thence downward along the anterior axillary fold. With the arm drawn across the body the posterior flap is outlined by an incision along the vertebral border of the scapula, which unites with the anterior incision along the lateral axillary fold. The arm is then swung back to its original position, the anterior incision is deepened and the pectoral muscles are divided. The arm is now brought forward again and the muscles of the posterior flap along the vertebral margin of the scapula are divided. Care is taken to clamp, sever, and ligate the transverse cervical artery before it retracts, if this has not been done at an earlier stage. When the scapula has been freed of its muscular attachments the amputation is complete. The vessels are ligated with nonabsorbable suture material. Drains may be used at the discretion of the surgeon. Skin grafting is resorted to only when the size and the location of the tumor and the degree of skin involvement make closure impossible.

Kocher's Anterior or Pectoral Approach

The only difficulty encountered during the Berger operation is the exposure of the subclavian vessels; this is a time-consuming stage in the procedure. The anterior approach suggested by Kocher avoids this difficulty. After the middle third of the clavicle has been resected, the ligation of the subclavian vessels is postponed until the anterior incision is carried through the pectoral muscles into the axilla. This part of the dissection is similar to the same phase in a radical mastectomy as the axillary artery and vein come immediately into view. With the more adequate exposure thus afforded, the subclavian vessels are more readily located and the underlying artery mobilized and ligated without the previous hazard of injuring the overlying vein. From this point on, the operative technic is identical to that previously described.

SHOULDER JOINT DISARTICULATION

Indications

The vast majority of primary malignant tumors involving the humerus affect the upper third of the bone; many of these are therefore unsuitable for shoulder joint disarticulation and require an interscapulothoracic amputation. However, there are instances where the tumor is medullary in origin and by clinical and roentgenographic examination it is apparent that the overlying soft tissues are free of the disease. In such cases, if resection-and-

bone-graft is not deemed practical, a shoulder joint disarticulation has its place. This operation is likewise suitable for the rare examples of tumors that occupy the distal half of the humerus. In these cases there is little reason to remove the scapula as well as the arm and therefore the less radical procedure is preferable. However if doubt exists as to which is the safer procedure the more radical interscapulothoracic amputation should be selected since there is little functional advantage in the more conservative operation.

Technic of Operation

We prefer to perform this operation under a tourniquet held in position by Wyeth pins. The posterior pin passes upward through the lower part of the posterior axillary fold and emerges close to the posterior aspect of the tip of the acromion; the anterior pin enters the anterior axillary fold at a corresponding position and comes out just anterior and medial to the acromion. Rubber tubing for the tourniquet is fastened as depicted in Figure 297.

The classical Kocher incision (racquet) begins over the clavicle and passes downward lateral to the coracoid process dividing the anterior fibers of the deltoid. The cephalic vein is ligated together with the acromial branches of the acromiothoracic artery. The capsule is slit along the lesser tuberosity. The long head of the biceps, latissimus dorsi, subscapularis, pectoralis major, and teres major are divided close to their insertions. The capsule with the insertions of teres minor, supraspinatus, and infraspinatus is freed from its attachment to the bone. The anterior and posterior circumflex arteries are ligated and the arm removed. The brachial vessels are identified and secured with double ligatures and the nerve trunks injected with 95 per cent alcohol. The tourniquet is then loosened and all bleeding points ligated, after which the Wyeth pins are removed and the wound closed by suturing the tendons and muscle stumps across the glenoid. The skin wound is approximated with silk and a snug pressure dressing is applied with adhesive or elastoplast. If the tip of the acromion process is divided with a bone-cutting instrument and removed a much better cosmetic appearance is obtained.

AMPUTATION ABOVE THE ELBOW

Few opportunities are presented to perform amputation above the elbow since malignant tumors of the forearm bones are of rare occurrence. When this operation is required, as much of the upper arm should be preserved as is consistent with complete extirpation of the tumor.

Technic of Operation

The circular type of amputation is best. A tourniquet is applied above the biceps muscle belly. The flaps of skin and fascia are dissected upward

to the level at which muscles are to be divided. This distance is roughly half of the diameter of the limb at the level at which the bone is to be severed. The muscles are cleanly cut down to bone and gently retracted for a distance of one and one-half inches, exposing the bone at the level at which it is to be separated. While the saw is being used the soft parts are easily retracted by an assistant using a large abdominal pad. Ligation of the vessels and disposition of the major nerve trunks is effected as in any amputation. Skin closure should be accomplished so that there is neither undue tension nor redundancy of the flaps.

AMPUTATION BELOW THE ELBOW

This level is seldom required for amputations for malignant tumors of bone. It should be reserved for those extremely rare malignant neoplasms of the carpal or metacarpal bones. It is suitable for a synovioma arising in a flexor tendon sheath in the palm of the hand.

The technic is so similar to that described for the preceding amputation that no further description is deemed necessary.

Partial Amputation of the Hand

Under exceptional and rare circumstances it may become necessary to remove part of the hand for a tumor of bone. The only instances in which the author found this procedure indicated are illustrated in Figures 269, page 463, and 280, page 471.

Amputation of Fingers

Primary malignant tumors of the fingers are of exceptional rarity. We know of no case in American literature nor of any records of such in the Bone Sarcoma Registry of the American College of Surgeons. We have personally observed but one case (see Fig. 269, p. 463). For this reason amputation of the fingers is seldom a justifiable measure for the treatment of tumors of bone. An exception is noted in Figures 80 and 81, pp. 165-166, which illustrates a giant cell tumor of the distal phalanx in a 13-year-old Negro male, in which case amputation through the proximal phalanx was performed.

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SECTION EIGHT

Radiation Therapy

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52. PHYSICAL FACTORS INVOLVED IN THE IRRADIATION OF TUMORS OF BONE

IN ANY STUDY OF THE EFFECT OF RADIATION THERAPY ONE SHOULD CONSIDER not merely the radiation delivered to the surface of the patient's body but also the depth dose or the dose received by the tissues one is endeavoring to treat. Roentgen-ray machines are commonly calibrated to show the number of roentgens per minute which will be registered by a small measuring instrument suspended in air at a stated distance from the target of the tube. If the instrument is laid on the surface of a patient's body the reading will be higher than that in air, owing to the radiation scattered back from the underlying tissue. If the instrument is inserted in a body cavity, the reading will usually be lower than that in air because part of the incident radiation is absorbed in the overlying tissue. On the other hand, if the instrument is only a very short distance below the surface the reading may be equal to, or higher than, that in air because the radiation scattered back from below may be more than that absorbed above. The readings of the instrument on the skin or at a depth in the tissues afford a measure of the skin and tissue doses respectively.

The differences between air dose and skin and tissue doses are often considerable. The skin dose is influenced by the quality of the radiation used, the size of the field, and the thickness of underlying tissue. The tissue dose is influenced by the above factors and also by the distance from the tube and the thickness of overlying tissue. It is not possible, in general, to calculate a tissue dose from theoretical consideration of the factors involved. Empirical measurements of skin and tissue doses under a great variety of conditions have, however, been published in the radiological literature. A discussion of the effects of various factors on tissue dose will be found in Chapter XII of *Physical Foundations of Radiology* by Glasser, Quimby, Taylor, and Weatherwax (Hoeber, 1944). By the use of the tables in the Appendix of this book, it is possible to calculate the tissue

doses obtained under most of the conditions commonly employed in roentgen therapy.

For instance, for 200-kilovolt roentgen rays, with 0.5 mm. copper filter and 50 cm. target-skin distance, the dose at various depths for 3 different field sizes is given in the above mentioned tables as follows:

Field area in sq. cm. Air dose, %	50 100	100 100	225 100
Depth in cm 0 (= skin)	Tissue dose in % of air dose		
2	130	136	144
5	112	122	134
10	72	82	97
15	33	41	51
	18	24	31

Suppose that it is necessary to treat a lesion in the mid-portion of the radius of a child. Assume that the lesion is equidistant from the palmar and volar surfaces of the arm; then the depth of the center of the tumor below the skin will be about 2 cm. If a 5 x 10 cm. field is used, the dose to the tumor will be 112 per cent of the air dose, or $112/130 = 86$ per cent of the skin dose. If two such fields are outlined, the total dose to the tumor will be $2 \times 86 = 172$ per cent of the dose to the skin of each field. In contrast, a lesion of the upper femur of an obese individual may be 15 cm. below the skin. From a 15 x 15 field the tumor will receive 31 per cent of the air dose, or $31/144 = 22$ per cent of the skin dose. Since the limb is large it may be possible to outline four such 15 x 15 cm. fields, but even so the dose received by the tumor from all four fields will be only $4 \times 22 = 88$ per cent of the dose to the skin of each field.

One of the principal limiting factors in the amount of radiation which may be used therapeutically is the tolerance of the skin. In the above examples, if the treatment is pushed to the limits of skin tolerance, the tumor in the small limb will receive about twice as much radiation as the tumor in the large limb. It is thus evident that even when, as in these illustrations, the method of cross-firing is used, the amount of radiation which can be delivered to the skin safely bears no close relation to that which will be received by the tumor. In the first of the above illustrations the tumor dose from each field was 112 per cent of the air dose while in the second the tumor dose was only 31 per cent of the air dose. Hence, in evaluating the effects of radiation therapy, a consideration of the air dose alone will lead to entirely misleading conclusions. To obtain a true picture it is essential to calculate tumor doses.

The illustrations given do not take into account exit dose, asymmetrical

position of the tumor, and other variables. A detailed consideration of all the factors entering into the calculation of tissue doses cannot be given here. The reader wishing further information on the subject should consult the textbook referred to, or other standard works on radiology.

In the following study of the results of radiation therapy of bone tumors, the figures given are tumor doses unless otherwise stated. Calculations were made by the use of standard tables. The chief source of error in such calculations is in obtaining accurate measurements of the depth of the tumor below the skin. In the majority of cases the depth was obtained by measurement of X-ray films. The error in such cases did not exceed 10 per cent. When suitable films were not available it was necessary to estimate the depth of the tumor by measurements of the patient or of another individual of the same build. This involved an error of approximately 20 per cent. In most cases the dose was calculated at the center of the tumor. In a few cases where it was evident that some portions of the tumor received much more radiation than others, the dose was calculated for the portion of the tumor which received the least radiation.

The rate of the radiation is an important factor for the greater the rate the more destructive the effect. Heavy doses given at a rapid rate may destroy all tissues while the same amount given at a slower rate may exert a selective action which effects some tissues more profoundly than others. There is also some evidence that this selective action is due in part to the more rapid recovery of normal tissue and it is the basis upon which much of the roentgen therapy of tumors depends.

Radiation effect, therefore, depends upon the amount and the intensity of radiation that is absorbed and upon the size of the area exposed.

Bone changes following substantial doses of radiation do not attract attention as readily as do changes in soft tissue. This is due in part to the relatively acellular nature of bone in which minor changes in the chemical and physical structure may produce but little alteration in the roentgenographic appearance. Histologic changes likewise may be slight. The only distinction between viable and nonviable bone may lie in slight differences in the appearance of the osteophytes and variations in the staining properties. Yet if infection occurs or if trauma is sustained, the profound biologic damage that irradiation has produced is brought to light by the distinct impairment of resistance and delayed healing.

Histologic changes due to prolonged or intense therapeutic irradiation of bone or to chronic radium poisoning have been described by Ewing, Martland, and others. There is need for much more investigation of the effects of roentgen therapy correlated with dosage factors, time interval, subsequent course, and end-results. Clinicians should be encouraged to

report single cases on which they have complete data including roentgenographic and pathologic findings. In addition, information on long survivals of treated cases together with operative and autopsy material would be helpful.

Ewing's observations on the histologic changes in human bones following extremely heavy doses of radiation by roentgen rays or radium pack are of interest. In a case of spontaneous fracture amputated eighteen days later none of the expected inflammatory reaction or evidence of repair was found. He states:

In the portions of hard bone taken from the shaft away from the tumor, the cell spaces appear to be larger and more irregular, the canaliculi are larger, widened, very irregular, reduced in numbers, and the communications between adjoining cells are very imperfect. Numerous abnormal spaces appear between the lamellae. The lamellar substance appears very hyaline and brittle. . . . It is admissible to conclude that these changes signify severe degeneration of the bone cells, destruction of many cell processes and closure of many canaliculi and changes of undetermined nature in the lamellar substance.

Microscopic study of animal material in cases where bone growth was stunted by radiation reveals early alteration of the cartilage cells and disorientation of endochondral ossification as the principal findings.

Cartilage, as affected by radium and roentgen rays, should be considered under two headings; hyaline or joint cartilage, and epiphyseal or growth cartilage. Hyaline cartilage in such locations as knee, shoulder, and hip is relatively resistant to irradiation. When located in the ear, nose, or larynx, however, it can be damaged to such an extent that complicating perichondritis may prove to be serious or even fatal. Its tendency to develop late, even after several years, is a misleading one. Reports of histologic findings in these cases are in the main scanty and not proportional to clinical observations.

Two distinct types of late destructive effect of heavy radiation for bone tumors are recognizable. In the first, the skin and soft parts are damaged with refractory ulceration and sloughing. The process may or may not extend down to bone. Prolonged ulceration with inevitable secondary infection has been accompanied by advanced amyloidosis. Vigorous efforts may be necessary to remove devitalized tissue and to cover with skin. Pedicled grafts may be required.

A second late effect is chiefly concerned with radiation osteitis and while the skin and overlying soft tissues are often profoundly altered, ulceration has not yet occurred. Bone that is permanently damaged by excessive roentgen therapy is brittle and pathologic fractures may occur; its healing powers are seriously altered (see Fig. 299). Brittleness is a conspicuous feature here. Endosteal bone formation is prominent; atrophy and eburna-

tion are changes that occur later. Bone matrix is influenced by radiation though the mechanism of this alteration is little understood.

Necrosis in irradiated bone is followed by greatly prolonged sequestra-



FIG 299. Bone changes seen in both tibia and fibula following excessive doses of roentgen therapy, given for what was considered a low-grade fibrosarcoma of the tibia but which is now regarded as having been an area of fibrous dysplasia.

tion. Infection is a serious and stubborn complication. Marked disintegration may result. Fractures through irradiated bone heal slowly at best and fibrous union or nonunion is frequent.

53. EFFECT OF RADIATION ON BONE

THE RATIONALE OF RADIATION THERAPY IN TUMORS OF BONE AS IN TUMORS of other tissues is based upon the relative radiosensitivity of neoplastic tissues and normal tissues. Both tumor cells and normal cells are affected by doses of radiant energy which they absorb. This is true of all types of radiation, e.g., roentgen rays, radium, radioactive isotopes, or any other source of ionizing radiation.

Studying these effects under the microscope one may observe a slowing of the rate of mitosis, changes in the appearance of the chromosomes, swelling and vacuolization of the cytoplasm, pyknosis, and autolysis.

Unquestionably tumor cells do not all die following ordinary therapeutic doses of radiation; some recover either partially or completely. It is generally considered that the major factor in the favorable response of malignant neoplasms to radiation therapy is the change produced in the surrounding tissues (i.e. tumor bed). Among these is impairment of circulation from thrombosis of blood vessels which results from damage to endothelial cells, hyalinization of collagen fibers, and fibrosis. These alterations tend to wall-off residual, viable tumor cells and to prevent or inhibit their spread to adjacent surrounding tissues.

By and large the more primitive and undifferentiated the cells, the more radiosensitive the tumor; conversely the more adult and highly differentiated types are generally radioresistant. There are many exceptions to this rule and tumors of the same cell type do not always exhibit the same degree of radiosensitivity.

Warren has suggested three classes of responsiveness to the effects of irradiation. Those neoplasms which regress with doses which inflict little damage to nearby normal tissues he calls *radiosensitive*, those which regress only after doses which are moderately injurious to adjacent normal tissues are termed *radioresponsive*; and those which are not more susceptible than adjacent normal tissue and require for regression doses which will severely damage normal tissues near the tumor are considered to be *radioresistant*. Such doses may be estimated as follows:

Radiosensitive	2000 to 2500 r.
Radioresponsive	2500 to 5000 r.
Radioresistant	5000 r and over.

The accompanying table lists the various benign and malignant neoplasms of bone according to their radiosensitiveness.

However, while regression may be relatively complete and of long duration one must bear in mind that some tumors which are radioresponsive and others which are even radiosensitive as judged by the degree to which

TABLE XL
RADIOSENSITIVITY OF BONE NEOPLASMS

	BENIGN TUMORS	MALIGNANT TUMORS	OTHER BONE CONDITIONS
<i>Radiosensitive</i>	Giant cell tumor Bone cyst	Reticulum cell sarcoma Ewing's sarcoma Plasma cell myeloma Metastatic neuroblastoma	Kand-Schuller-Christian's disease Eosinophilic granuloma
<i>Radioresponsive</i>	Benign chondroblastoma Fibrous dysplasia Angioma	Metastatic thyroid cancer (some types) Hodgkin's disease in bone Some other metastatic cancers	
<i>Radioresistant</i>	Osteoma Chondroma Osteoid osteoma Adamantinoma Chordoma Nonosteogenic fibroma	Osteogenic sarcoma Chondrosarcoma Metastatic carcinoma (most types) Synovioma in bone Neurogenic sarcoma in bone	Hydatid disease of bone

they regress after exposure to low or moderately high doses do not remain dormant or actually die. After a lapse of many months to one or more years they may commence to grow again and eventually terminate in the death of the patient.

For example, Ewing's sarcoma may disappear after a tissue dose of 3500 or 4000 r (and the patient may seem to be completely cured) only to recur at the site of previous therapy and continue to grow and to metastasize.

With experiences such as the one just cited it becomes necessary to revise our estimate of the total dose required to inactivate permanently and completely tumors of bone which by their immediate response must be considered as radiosensitive or at least radioresponsive.

54. INDICATIONS FOR ROENTGEN THERAPY

ROENTGEN THERAPY MAY BE USED IN THE TREATMENT OF EITHER BENIGN or malignant tumors of bone. In the former it is a definite method of therapy; in the latter it may be employed in the hope either of controlling the disease permanently or of accomplishing a measure of palliation by relieving pain, reducing or retarding the growth of the tumor, and prolonging life.

BENIGN TUMORS

Experience with roentgen therapy for benign tumors of bone has been somewhat disappointing and it is now felt that there are not many instances in which this method is desirable. There are but few lesions in which an efficacious dose does not tend to produce undesirable late effects upon normal bone and its soft-tissue coverings. In some instances it has been found possible to select a dose that will produce maximal beneficial results with a minimum of undesirable ones but unfortunately the same technic employed in subsequent cases has not always been productive of similar satisfactory results. This is especially true of the benign giant cell tumor.

It is certain that roentgen therapy has no real place in the treatment of benign tumors of chondromatous origin nor is it recommended for osteoid osteoma. Likewise we have largely abandoned its use for cyst and giant cell tumor in accessible locations (where the majority occur). The principal indication for roentgen therapy is giant cell tumor in inaccessible areas.

The undesirable late effects of irradiation of bone, particularly as regards overlying soft parts, adjacent joint structures, inhibition of bone growth, etc., have already been mentioned. They constitute valid arguments for withholding such treatment for accessible benign neoplasms of bone. Of greater importance is the possibility that there may later develop a malignant tumor (osteogenic sarcoma or chondrosarcoma) at the site of and presumably on the basis of the previous roentgen therapy. Cahan,

Woodard, Higinbotham, Stewart, and the author have published records of 11 cases in which this undesirable sequel has occurred. From these cases the following have been selected as examples:

Case 1

J.B. Past History: had pneumonia in childhood.

Present Illness: Fourteen years prior to his admission, when the patient was 9 years old, he had a fist fight with some other boys and was struck on the right shoulder but developed no subsequent pain, swelling, or incapacity.

About one year later, at the age of 10, while he was ice skating, he fell backwards as his feet slid forward and the force of the fall was received on both elbows, principally the right. Pain in the right arm followed immediately and, although there was no external evidence of injury, it gradually became stiff. After two weeks of persistent pain and difficulty in putting on and removing his coat, he saw his family doctor who took X-rays of his right arm. The patient's father was told that the boy had a bone sarcoma and immediate amputation was advised. This was refused and he was taken to another hospital where radiotherapy was given as follows:

From Jan. 18 to May 23, 1922, through 3 portals (probably anterior, posterior, and lateral), in doses of 550 r (in air), he received a total of 2750 r x 3. The factors were: 130 Kv, 0.5 mm. Cu, (TSD and Ma. not mentioned).

On July 11, Sept. 25, and Dec. 12, 1922, an additional 1100 r was given to 2 portals and 550 r to the third portal. The factors were: 200 Kv, 0.75 mm. Cu, (TSD, Ma, and size of portal not mentioned).

It was finally estimated that this patient received a bone dose of between 6000 and 9000 r.

Course: The patient stated that, following the above, the stiffness increased so that the X-ray treatments were abandoned. He went to another, "very reliable" hospital and on January 18, 1923, had a curettage of a "bone cyst of the proximal end of the humerus in the region of the epiphyseal line" (no X-ray available).

Gross Pathological Description: "Curettings consist of spicules of bone, partly organized blood clots, bits of cartilage, and strips of thin, smooth, white shining membrane resembling synovial membrane. All of the curettings were examined under the hand lens and identified as above. The appearance of the tissue did not suggest new growth."

Microscopic Description: "Several pieces of curetted material, differing somewhat in appearance but representative of all of the curettings, were sectioned. Some show partly organized blood clot, others show a chronic inflammatory tissue. Some of it is old, dense fibrous tissue, some is quite recent, soft, cellular, and containing many new capillaries and granulation tissue. *There is no evidence of neoplasia.*" An original section received from Post-Graduate Hospital was reported by the Memorial Hospital pathologist as bone cyst, probably secondary to a localized osteomyelitis.

Course: Following this curettage, the arm was placed in traction and one day was felt to snap. X-rays showed a fracture at site of lesion and the patient was told that the arm would never heal. From his own doctor he received massage

for the following twelve months and developed a flail joint at the site of fracture, with deformity and very limited function.

For the next ten years he went without any treatment. In June, 1934, while helping a friend move furniture, he felt a sharp pain over the anterior surface of the right shoulder. He did not consult a doctor, but maintained this extremity at constant rest.

In August, 1934, he was seen at Memorial Hospital for the first time, but no evidence of tumor was observed and he was referred to an orthopedic hospital where no therapy was administered. In March, 1935, he was referred back to Memorial Hospital because it was felt that he now had a tumor which had become malignant. He had lost 38 pounds in the six months' interval.

The patient appeared emaciated and pale. There was marked shortening of the right arm which measured 23 cm. in length as compared with 38 cm. on the left. An 8 x 10 cm. bulge was present over the anterior portion of the right shoulder joint, extending over the pectoralis major. Just over the head of the humerus there was a 2 x 1 cm. localized swelling which was fluctuant and inflamed. No motion could be elicited about the shoulder, but false motion was present below the joint. The overlying skin over an area 18 cm. in length was roughened, thickened, and telangiectatic, presumably from previous irradiation (see Fig. 300 A and B).

Roentgenogram on admission, March 18, 1935, showed "the remaining portion of the humeral head has been largely destroyed along with the upper one-half of the shaft" (see Fig. 300 C). An aspiration biopsy was diagnosed as "spindle cell sarcoma—probably one of medullary spindle cell osteogenic type." Blood chemistry at this time was: phosphatase, 5.6 units; phosphorus, 4.23 mg./100 cc; calcium, 11.0 mg./100 cc.

On Mar. 25, 1935, a right interscapulothoracic amputation was performed (see Fig. 300 D). The specimen was reported as "medullary spindle cell osteogenic sarcoma. Nodes free."

He was given twenty-five injections of Coley's toxin subsequent to this. His alkaline phosphatase increased to 14.0 units and the phosphorus to 5.11 mg. per cent two weeks after operation but returned to normal a month later and has remained so ever since.

On February 26, 1947, he was seen in follow-up and no evidence of disease was demonstrable.

Interval Between Roentgen Therapy and Development of Sarcoma: Thirteen years.

Case 2

I.W. Past History: non-contributory.

Present Illness: When patient was 8½ years old his parents noticed that the child limped. After two months without improvement, the patient was referred to Memorial Hospital on October 16, 1929, after he had had a preliminary examination and Roentgenographic study by his family physician. *Physical examination* was negative; no distortions noted.

A stereoscopic view of the right hip on Oct. 16, 1929, revealed evidence of

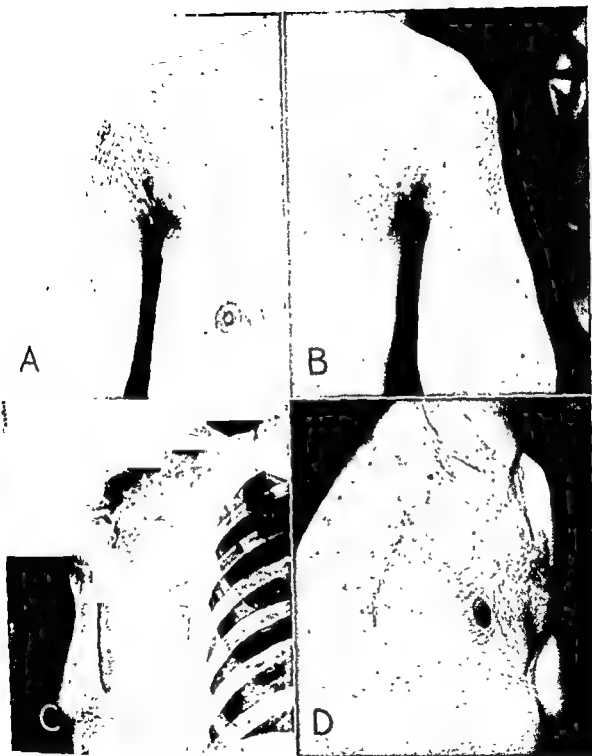


FIG. 300. A and B, Osteogenic fibrosarcoma arising in an old bone cyst treated fifteen

years. C and D, Appearance of patient following interscapulothoracic amputation. Patient is free of disease more than ten years. (See "Sarcoma arising in irradiated bone." *Cancer* 1:3, 1948, case 4.)

a process involving the neck of the femur, apparently medullary in origin (see Fig. 301 A). This may be considered to have been a bone cyst.

Roentgen therapy was begun in October, 1929, when the right femur received



FIG. 301. A, Bone cyst of upper femur at age of eight. Case was treated with heavy roentgen therapy. B, Appearance fifteen years later. The lesion is now malignant and the patient died of pulmonary metastases. (See "Sarcoma arising in irradiated bone." *Cancer* 1:3, 1948, case 6.)

600 r to anterior and posterior 4 x 4 cm. portals. Two months later he received repetition of the previous cycle. The factors in both instances were: 175 Kv, 0.5 mm. Cu filter, 50 cm. TSD. In March, 1930, he had 590 r each to anterior and posterior femoral portals measuring 8 x 6 cm. and 6 x 4 cm. respectively. The factors were: 185 Kv, 0.5 mm. Cu filter, 50 cm. TSD.

It is now estimated that the dose to the center of the tumor was 1550 r.

Course. A film made in April, 1930 (not now available) was described as showing "further improvement (calcification?) when compared with previous film."

From March, 1930, until September, 1944, he was asymptomatic. He joined the armed forces in 1943 and served two years in the infantry. In September, 1944, he began to notice stiffness of the entire right leg each morning on arising, but marching would relieve the stiffness; a few weeks later pain and stiffness appeared in the right hip, accompanied by difficulty in walking. A diagnosis of neuritis was made and bed rest advised. At one Army hospital a film was diagnosed "fibrocystic disease of the right femur." At another hospital a curettage was proposed, but instead he was given 1800 r to each of 2 8 x 15 cm. portals, anterior and posterior, directed to the upper femur. Factors: 200 Kv; 15 Ma.

50 cm. TSD, filter Thoracur. This treatment was administered between Apr. 23 and May 15, 1945.

There was temporary relief of pain, but this returned in a few months and his disability was even more marked.

He was admitted to Memorial Hospital on June 20, 1945. A roentgenogram (see Fig. 301 B) was made which showed areas about the right hip which were considered to be suspicious of malignant tumor. The serum phosphatase, calcium, and phosphorus were normal.

On Sept. 6, 1945, a specimen of bone was obtained from the femur which was reported as "low grade chondrosarcoma." A chest plate showed numerous round opacities typical of metastases, and the patient died in February, 1946.

Interval Between First X-ray Therapy and Sarcoma: Seventeen years.

Case 3

B.M. Past History: non-contributory.

Present Illness: In 1933, thirteen years before his admission to Memorial Hospital, the patient fell and fractured the upper portion of the left humerus. Roentgenogram taken showed a rarefied area at the fracture site (see Fig. 302 A) which was considered benign, the choice lying between a bone cyst and fibrous dysplasia although an enchondroma and nonosteogenic fibroma were also mentioned as possibilities.

Roentgen Therapy: From February to June, 1933, he was given five treatments of 450 r each; two treatments were to anterior portals, two were to posterior portals, and one to a lateral portal. Factors were: 140 Kv, 4 mm. Al., TSD 30 cm., 4 Ma.

In January, 1934, he had one treatment of 700 r to a 10 x 6 cm. lateral portal, using 198 Kv, 0.5 Cu filter, 50 TSD, 30 Ma.

In July, 1934, he had 800 r to a lateral portal, and from June, 1937, to October, 1937, he had six treatments to the lateral portal at intervals of two months between groups of three treatments. These treatments in 1934 and 1937 were with 200 Kv, 0.5 Cu filter, 35 cm. TSD, 6 cm. portal.

In all, it has been estimated that the center of the tumor received a total dose of 5580 r in four years.

He remained symptom-free for the next nine years and joined the RCAF as a pilot, remaining on active duty for four years. In June, 1946, he fractured the left humerus again after a trivial blow. The arm was placed in plaster but failed to show bony union. Films revealed calcium deposits in the soft tissues. The condition of the arm became progressively worse and more painful. He was admitted to Memorial Hospital on Sept. 7, 1946. Examination revealed that the left upper arm was markedly swollen and tender, and the overlying skin showed the effect of previous irradiation by dryness, depigmentation and telangiectasia, and marked fibrosis. There was atrophy of the anterior portion of the arm and all movements about the shoulder were markedly limited (see Fig. 302 E).

On Oct. 9, 1946, an open biopsy was reported as osteochondrosarcoma, fairly low-grade. Accordingly, on Oct. 18, 1946, an interscapulothoracic amputation of

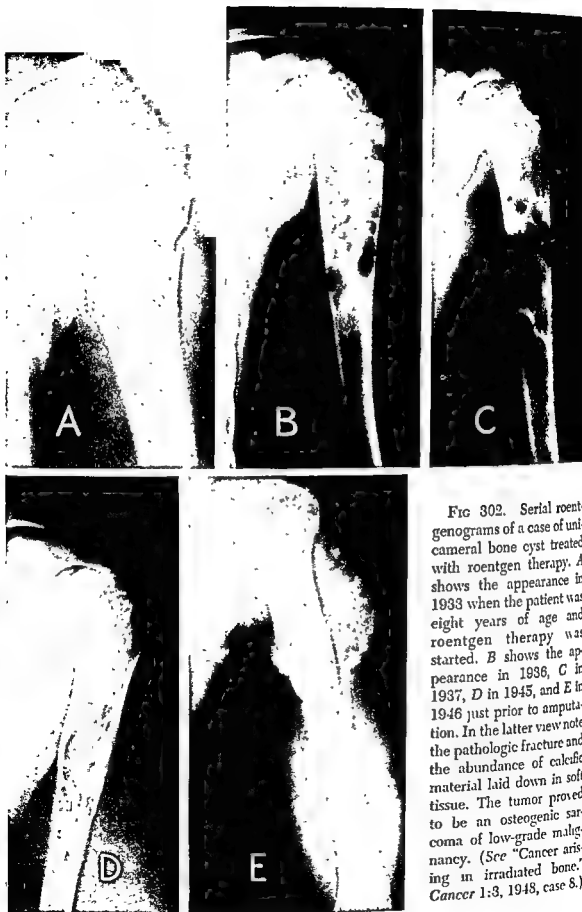


FIG 302. Serial roentgenograms of a case of unicameral bone cyst treated with roentgen therapy. A shows the appearance in 1933 when the patient was eight years of age and roentgen therapy was started. B shows the appearance in 1936, C in 1937, D in 1945, and E in 1946 just prior to amputation. In the latter view note the pathologic fracture and the abundance of calcific material laid down in soft tissue. The tumor proved to be an osteogenic sarcoma of low-grade malignancy. (See "Cancer arising in irradiated bone." *Cancer* 1:3, 1948, case 8.)

the left upper extremity was performed and the specimen confirmed the original biopsy diagnosis.

In May, 1947, a lump appeared beneath the scar near the point where the clavicle had been divided with the Gigli saw at the time of the amputation. He was reoperated upon May 5, 1947, and the clavicle again severed near the sternal notch so that the mass could be removed as a whole. Report of this specimen showed it to be microscopically similar to the humeral lesion, i.e., chondrosarcoma. Death from metastasis occurred.

Interval Between X-ray Therapy and Development of Sarcoma: Thirteen years.

Case 4

F.B. Past History: pleurisy, left side, 1934.

Present Illness: In October, 1934, the patient turned over on a motorcycle, landing on his right shoulder and sustaining a fracture about 4 cm. below the head of the humerus. At another hospital, the arm was strapped in place for seven weeks, after which time it was gradually returned to use although it never seemed to regain its full strength.

One and a half years later, the patient sustained another fracture of the right shoulder without gross evidences of trauma. After roentgenographic examination made by his physician, the arm was immobilized with adhesive strapping; infrared treatments were administered and finally roentgen therapy was given. The films showed what was described as a "giant cell tumor of the head and upper portion of the shaft of the right humerus."

Between Apr. 21 and May 27, 1936, the patient received eight treatments of roentgen therapy to each of 3 portals (superior, anterior, and posterior) measuring 10 x 15 cm. The factors were: 200 Kv, 0.5 mm. Cu filter and 2 mm. Al, 40 cm. TSD. This was a total of 1440 r, measured in air, to each of the three portals. *It was estimated that the proximal margin of the tumor received 3070 r, and the distal margin, 2480 r.*

Course: Ten days after his last treatment, on June 17, 1936, he was admitted to Memorial Hospital. Physical examination showed the skin over the entire right shoulder to be tanned and desquamating. No actual blistering was observed. Pressure over the head of the humerus caused considerable pain. Patient was able to raise the arm, but pain was experienced when it was abducted beyond 90 degrees. Some enlargement about the right shoulder was noted.

Roentgenogram (see Fig. 106 A, p. 192) on June 17, 1936, was reported as "giant cell tumor, upper end of right humerus, apparently growing rather rapidly."

An aspiration biopsy performed at this time showed "benign giant cell tumor." He was placed in a modified Velpeau dressing, immobilizing the entire shoulder with the arm abducted at 90 degrees and flexed at 90 degrees at the elbow.

Roentgenogram made November 10, 1937 (Fig. 106 B, p. 192), showed dense ossification of upper portion of the shaft of the humerus, and physical examination revealed about 50 per cent of shoulder function.

The patient stayed away from the Follow-Up Clinic for seven years. He was readmitted to Memorial Hospital on Dec. 17, 1946, with a history of having

noted pain in upper arm and shoulder for two weeks previously, with increasing limitation of motion and increase in bulk. A soft, tender swelling was noted anteriorly on the upper arm three days before admission. Examination of the upper arm presented a firm, central tumor mass which was slightly tender.

An aspiration biopsy was performed and the pathologist reported "believe this will turn out to be malignant giant cell tumor. Nuclei getting atypical, and in the clot no giant cells are seen."

Roentgenogram on Dec. 17, 1946 (Fig. 106 C, p. 192), showed "cortical destruction present for about 3 inches of the upper portion of the shaft of the humerus with the formation of a soft tissue mass and very slight periosteal change. There has been decalcification in the region of the old giant cell tumor. The process is in intimate association with the acromion process."

On Dec. 23, 1946, an interscapulothoracic amputation of the right upper extremity was done and the pathological report was as follows: "*Gross:* The point of interest is at the upper end of the humerus where the anatomical head has been largely replaced by extensive tumor growth, measuring 6 x 7 cm. It is worthy of note that the overlying skin in this area is said to have been treated by irradiation at an earlier period in the patient's history but does not show scarring or telangiectasia, or any evidence of radiation changes at this time. The joint capsule appears to have been ruptured at one point, but it is not clear whether this was due to tumor or associated inflammatory and perichondritic changes. The tumor extends out into the soft tissue and has invaded the deltoid muscle until a shell of the latter muscle, approximately 2 cm. thick, is all that remains, bulging laterally and covering the tumor mass. There are numerous soft fleshy nodes in the axilla, none over 1.5 cm. in diameter, and all appearing uninvolved by the tumor process. There is a small pathologic fracture tangentially through the articulating surface of the humerus, but there is no complete transverse fracture producing preternatural motion."

Microscopic by Dr. Stewart: "There are small residual foci that retain the structure of giant cell tumor which do not look malignant. However, these areas merge with fully malignant osteogenic sarcoma which is highly cellular and pleomorphic and which here and there produces small foci of atypical bone and cartilage. This is not the expected evolution of a giant cell tumor which becomes malignant and, although there is no proof, it suggests to me that this is a radiation osteogenic sarcoma."

Course: On Mar. 5, 1947, a chest film was negative and there were no other evidences of disease. However by May 15, 1947, there were extensive pulmonary metastases.

Interval Between X-ray Therapy and Sarcoma: Ten years.

PRIMARY MALIGNANT TUMORS OF BONE

OSTEOGENIC SARCOMA AND CHONDROSARCOMA

Since roentgen therapy as a possible curative agent must be restricted to those tumors of known radiosensitivity, and in view of the known radioresistance of osteogenic sarcoma, fibrosarcoma, and chondrosarcoma, it is apparent that in these types there is little place for this form of therapy

except as a palliative measure, where the tumor is inoperable, or where consent for operation cannot be obtained. In some instances it is advisable to commence therapy while the patient or his parents are making up their minds about granting permission for an operation. In this same category should be placed the malignant form of giant cell tumor.

ENDOTHELIOMA (EWING'S SARCOMA) AND RETICULUM CELL SARCOMA OF BONE

The relative radiosensitivity of Ewing's sarcoma and primary reticulum cell sarcoma of bone places these closely allied tumors in the group in which there is a reasonable prospect of being able to deliver a dose of roentgen rays sufficient to cause permanent control of the local lesion. This being the case roentgen therapy seems preferable to radical surgery for these tumors. It can fairly be assumed that the subsequent distant metastases would have developed even if immediate amputation had been performed.

The constancy with which Ewing's sarcoma spreads to lungs and other bones regardless of the method by which the primary tumor is treated makes one loth to amputate. In treating the lesion with roentgen rays it should be remembered that moderate doses produce only temporary control; for permanent inactivation of the disease it is necessary to deliver a rather high total dose to the center of the tumor (see page 309).

The reaction of reticulum cell sarcoma of bone to roentgen therapy is similar to that of Ewing's sarcoma. Fortunately it has the tendency to disseminate less early and here the prospect of a cure is considerably brighter. This tumor, therefore, may be regarded as the most favorable of all primary malignant neoplasms of bone for roentgen therapy.

LIPOSARCOMA OF BONE

The rarity of primary liposarcoma of bone makes it impossible for one to render an opinion on its susceptibility to, or its successful management by, roentgen therapy. Further data are required. Meanwhile we do not feel justified in advocating its use in preference to amputation in operable cases.

PLASMA CELL MYELOMA

The multiplicity of areas of involvement in plasma cell myeloma coupled with the completely hopeless prognosis render this disease a most difficult one to treat. Surgery has no place here and radiation therapy is purely palliative. Nevertheless much can be accomplished by judicious roentgen therapy directed to the major symptom-producing areas, using moderate doses. Where pathologic fracture has occurred union may follow provided the dose used is not great enough to depress the healing power of bone. Since these patients often require treatment of a number of separate areas and since the hemopoietic activity of the bone marrow is frequently de-

pressed by replacement of normal cells with plasma cells, one should avoid exposure of large areas and heavy total dosage.

METASTATIC CANCER OF BONE

In bone neoplasms the principal field for roentgen therapy is that of metastatic cancer. Excluding castration or sex hormone therapy in cases of skeletal spread from prostatic or breast carcinoma, or use of radioactive iodine in selected cases of metastatic thyroid cancer, it is the only method of treatment that offers any hope of benefit. Its therapeutic effect may be marked and of considerable duration, moderate and of short duration, or so slight as to be disregarded. Unfortunately one cannot always predict which cases will show a worthwhile response. This is true even when the histologic nature of the individual tumor is known. The inference, therefore, is that every case should be irradiated at least until the effect is determined, thereafter the treatment can be continued for other areas of involvement or abandoned as not worthwhile. Since a cure in these cases is out of the question excessive doses should be avoided, the aim being to alleviate symptoms and to restrain tumor growth while permitting bone to regenerate. Doses in the neighborhood of 1200 to 1500 r calculated for the depth of the tumor-bearing portion of the bone are usually sufficient.

METASTASES FROM BONE SARCOMA

With rare exceptions bone sarcoma tends to metastasize to the lungs rather than to other viscera. We have reached the conclusion reluctantly that it is inadvisable to irradiate pulmonary metastases from fibrosarcoma, osteogenic sarcoma, and chondrosarcoma. The response seldom seems to justify such procedure. On the other hand marked regression of pulmonary foci from Ewing's sarcoma may be obtained with such regularity as to make it advisable to irradiate such areas routinely. Metastases from reticulum cell sarcoma of bone respond in a similar manner. Palliative treatment of Ewing's sarcoma metastases in other bones is also indicated.

TABLE XLI*

TISSUE DOSES IN ROENTGENS USUALLY REQUIRED TO INACTIVATE BONE TUMORS AND INHIBIT BONE REGENERATION

TISSUE	DOSE WITHOUT DEMONSTRABLE EFFECT	DOSE CAUSING TEMPORARY INACTIVATION	DOSE CAUSING PROLONGED INACTIVATION	DOSE CAUSING COMPLETE DEVITALIZATION
Osteogenic sarcoma	3000 r	3000-4000 r	4000-6000 r	? 8000 r 3000-4000 r
Reticulum cell sarcoma of bone				? 6000 r
Endothelioma of bone			3000-5000 r	1500-3000 r
Giant cell tumor	800 r		1000-2000 r	500 r
Regeneration of normal adult bone	2000 r	2000-3000 r	3000-4000 r	

* WOODARD, HELEN Q., and COLEY, B. L. The correlation of tissue dose and clinical response in irradiation of bone tumors and of normal bone. *Am. J. Roentgenol.* 57:464, 1947.

The treatment of primary skeletal sarcoma by means of irradiation rather than radical surgery has yielded disappointing results. Meyerding reported three five-year survivals of a series of 37 cases (9 per cent); Engels had 7 out of a series of 35 (20 per cent); Simmons had no prolonged survivals in a series of 6 cases; Brunschwig and Tschetter had only 1 out of 20 free of disease after five years, while another patient was alive but with evidence of active disease more than eight years later; four other cases were alive for more than three and less than four and one-half years with no clinical evidence of disease.

In a series of unselected cases of osteogenic sarcoma treated at Memorial Hospital by irradiation without amputation reported by the author in 1935, there was only one five-year survival. There were five other cases still alive at the time of the report, one of which had roentgenographic evidence of pulmonary metastasis. The effects of irradiation in this group of cases is shown in the accompanying table:

TABLE XLII
OSTEOGENIC SARCOMA—EFFECTS OF IRRADIATION

A. INOPERABLE CASES	37
Early effects:	
1. Subjective:	
Relief of pain	25
2. Objective:	
Improved function	17
Decrease in size of tumor	17
Radiographic decrease in size	3
Radiographic regeneration	5
Late effects:	
1. Tumor receded	3
2. Tumor remained stationary	2
3. Tumor continued to grow	22
4. Later growth of tumor after	
(a) apparent cure	1
(b) early recession	8
(c) stationary period	1
B. OPERABLE CASES	34
Early effects:	
1. Subjective:	
Relief of pain	19
2. Objective:	
Improved function	16
Decrease in size of tumor	14
Radiographic decrease in size	3
Radiographic regeneration, etc.	15
Late effects:	
1. Tumor receded	9
2. Tumor remained stationary	1
3. Tumor continued	12
4. Later growth of tumor after	
(a) apparent cure	0
(b) early recession	7
(c) stationary period	3

55. METHODS AND DOSAGE

IN PLANNING A COURSE OF ROENTGEN THERAPY FOR A MALIGNANT TUMOR OF bone the following factors must be considered:

1. The depth dose estimated for the center of the tumor, dependent upon the type of tumor and the desired objective (cure or palliation)
2. The extent of the bone requiring treatment which determines the length of the portals
3. The number of portals, dependent upon the location of the tumor—usually two but occasionally three or even four (see Fig. 303)
4. The number of treatments into which the total dosage is to be divided and the number of roentgens per dose
5. The interval between treatments
6. Voltage, target-skin distance, current, and filtration

Example: For an osteogenic sarcoma of the lower femur which appears to occupy a segment, 8 x 9 cm. and in which irradiation is planned because amputation has been refused, a typical outline is as follows: Anterior and posterior portals 8 x 12 cm.; daily treatments to alternate portals; 2400 r to each portal given in doses of 300 r each which require 8 exposures to each portal; 250 Kv., 50 cm. TSD, 30 ma. of current, 1.5 mm. copper filter.

Depending upon the depth of the tumor beneath the surface such a course of treatment can be expected to deliver from 50 to 75 per cent of the total skin dose to the center of the tumor and other portions would receive a somewhat higher percentage. If a third or a fourth portal can be utilized the depth dose can be correspondingly increased but due consideration must be paid to the effect upon the skin of the exit dose from the contralateral portal and to the danger of skin damage from overlapping.

When planning treatment it is the current opinion that the maximum dose should be outlined for the individual case without contemplating any further treatment. If control cannot be obtained by this method it is not to

be achieved by a later course of therapy and the danger to the skin of repeated courses is now well recognized.

While the technic for palliative roentgen therapy follows the same gen-

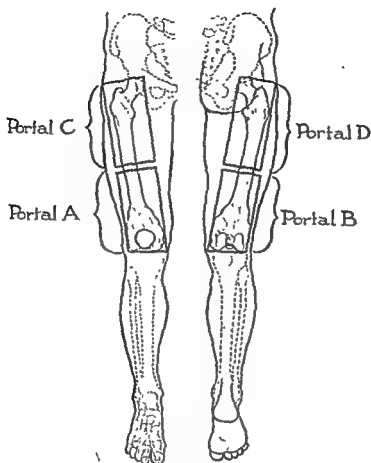


FIG. 303. Method of outlining portals for roentgen therapy. Portals A and B are ordinarily sufficient for tumors of the lower femur, C and D for those of the upper femur; however, particularly in extensive lesions of Ewing's sarcoma, the entire shaft may require irradiation which would involve the use of all four portals.

eral pattern exceedingly large doses are not desirable for several reasons: *first*, because with no possibility of a cure the risk of skin and soft-part damage is unjustified; *second*, because the aim is to relieve symptoms and less than maximal dosage will generally afford as much palliation as will the largest conceivable safe dose.

When dealing with primary bone sarcoma that has shown no evidence of metastases greater risks of damage to an extremity are justified than when dealing with metastatic cancer in bone or with a condition such as multiple myeloma.

When roentgen therapy is employed for giant cell tumor still greater caution is needed to avoid damage to the skin and soft parts, including the synovial membrane of the adjacent joint. This particularly applies to

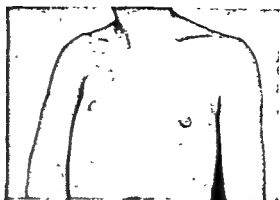


FIG. 304. Effect of heavy radiation on bone growth. Patient's right clavicular region was treated with heavy roentgen therapy at the age of one and a half years for an endothelioma of the clavicle. Note the greatly foreshortened shoulder, the discrepancy in the length of the clavicles, and the underdevelopment and shortened humerus.

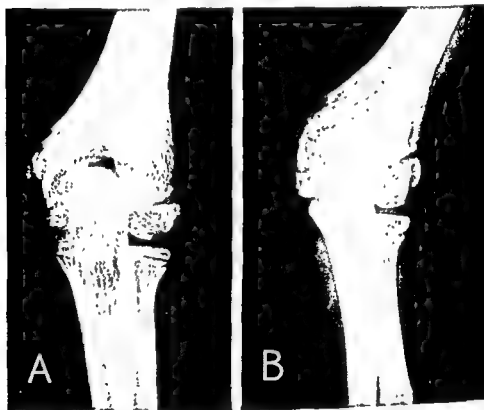


FIG. 305. A, Appearance of normal elbow in a 13-year-old male. B, Appearance of opposite elbow thirteen years after radiation therapy given for extensive hemangioma of the skin of the elbow. 1600 r given in a period of one month in doses of $400 \text{ r} \times 4$, and ten months later gold seeds of radium emanation were inserted which gave a total of 332 mc. hours. The effect on the tumor was most satisfactory but this photograph shows the pronounced disturbance of growth at the epiphyseal line on the radial side which has resulted in increase in the carrying angle (30 per cent). The case illustrates the danger of radiation therapy for benign lesions which entails exposure of the growth centers of immature bone.

the bone itself which may be rendered brittle and may lose its regenerative capacity when subjected to doses that might be justifiable for malignant tumors.

For reasons already cited (see page 137), it is considered inadvisable to treat bone cyst with roentgen rays (see Figs. 304 and 305).

SUPERVOLTAGE THERAPY

When a million volt roentgen-ray machine is available it may be used in place of the usual 250 kilovolt apparatus. We have not been able to detect a difference in the results of the two technics which would justify our insisting upon the use of the higher voltage except in deeply seated tumors.

RADIUM THERAPY

Although in the decade from 1925 to 1935 many cases of bone sarcoma were treated by the radium element pack at 10 cm. distance, using doses up to 50,000 mg.h., the conclusion was finally reached that this agent offered little or nothing above that obtainable by high voltage roentgen therapy; it was regarded as an expensive, time-consuming, and inefficient method, and was abandoned at Memorial Hospital.

56. EFFECT OF RADIATION ON TUMORS OF BONE

THE SIGNIFICANCE OF RADIATION EFFECT ON INHIBITING OR ABOLISHING the regenerative capacity of bone is no doubt apparent to the reader. While doses which exceed this capacity may destroy the tumor they may at the same time cause such irreparable bone damage as to preclude the possibility of an ultimately useful limb; in fact they may later compel an amputation in order to rid the patient of a functionless encumbrance.

The accompanying table shows the effect of radiation on bone regeneration and bone growth. Radiation was used in a variety of lesions all of which were controlled for a period sufficiently long to permit of a study of the behavior of the adjacent uninvolved bone. The regenerative capacity of the bone was estimated by observing the degree of restoration of integrity and structure and the extent of mineralization. The doses given are those that were delivered to the central portion of the bone and not to the skin.

Inspection of the table shows that in the adult, doses up to and including 3000 r given in a single course of treatment during a period of a few weeks are tolerated by normal bone without serious permanent loss of regenerative capacity. Doses between 3000 r and 4000 r usually are followed by some evidence of permanent bone damage, although some patients, as cases 11 and 12, appear almost unaffected. The effect of successive courses of radiation delivered at intervals of several months, while cumulative, is not strictly additive, and larger total doses can be given in multiple courses than in single ones.

We have few data on the effect of doses between 4000 r and 5000 r but it is evident that, in the adult, doses in excess of 5000 r even when given over a considerable period, are usually followed by complete loss of regenerative capacity of bone. Cases 16 and 21 are conspicuous examples. A comparison of Case 5 with Case 17, and of Case 6 with Case 21, gives a striking illustration of the difference in the effect of moderate and large

TABLE XLIII. EFFECT OF RADIATION ON BONE REGENERATION*

CASE No	NAME	SEX	AGE	CONDITION FOR WHICH RADIATION WAS GIVEN	DOSE	EFFECT ON BONE REGENERATION
1	E. H.	F	54	Ca. met. to femur, primary unknown	1710 r	Good regeneration 1 yr.
2	F. K.	F	7	Endothelial myeloma fibula	1380 r 2 mos. 350 r 10 mos. 1100 r	Mineralization in adjacent normal tibia undamaged 3 yrs.
3	D. G.	M	40	Giant cell tumor 1, lower femur (roentgen diagnosis)	3000 r	Mineralization undamaged 7 yrs.
4	A. H.	M	25	Aggressive giant cell tumor upper right femur	3010 r	Good regeneration of bone despite radiation ulcer of skin 11 yrs.
5	C. H.	F	35	Giant cell tumor 1, lower femur (roentgen diagnosis)	860 r 10 mos. 2610 r	Mineralization slightly impaired 1 yr. then recovered. Regeneration undamaged 6 yrs. after last treatment, as shown by good union of traumatic fracture.
6	A. F.	M	26	Giant cell tumor 1, ilium (roentgen diagnosis)	700 r 4 mos. 1825 # 4 mos. 1080 r	Regeneration impaired but not abolished 14 yrs.
7	N. L.	F	51	Destructive lesion rt. upper femur, type undetermined	2880 r 3 mos. 1280 r	Regeneration impaired but not abolished.
8	W. B.	M	14	Sarcoma 1, scapula	3540 r 4 mos. 1730 r	Bone texture somewhat abnormal 8 yrs.
9	E. M.	F	18	Reticulum cell sarcoma right lower femur	3700 r	Bone regeneration impaired temporarily, but recovered in 3 yrs
10	E. R.	F	21	Giant cell tumor right radius	3800 r	Mineralization slightly impaired 2 yrs.
11	D. T.	F	28	Giant cell tumor neck 1, femur (roentgen diagnosis)	3910 r	Regeneration undamaged 7 yrs.
12	W. V.	M	30	Endothelial myeloma right femur	4185 r	Good regeneration 18 mos.
13	N. K.	M	32	Osteolytic lesion rt. tibia, type undetermined	3100 r 3 mos. 1190 r	Mineralization slightly impaired 8 yrs.
14	J. T.	F	8	Osteolytic lesion rt. ilium, type undetermined	5425 #	Moderation limitation of growth and impairment of mineralization 7 yrs.
15	R. H.	F	12	Endothelial myeloma right fibula	5730 r	Good regeneration 10 mos.
16	S. L.	M	65	Malignant melanoma right lower leg	5650 #	Regenerative capacity of bone underlying tumor apparently completely lost 2 yrs.
17	C. G.	F	28	Aggressive giant cell tumor left lower femur	2560 r 5 mos. 1890 r 5 mos. 1660 #	Regenerative capacity of bone apparently completely lost, large areas no longer viable at amputation 5 yrs. after last treatment
18	A. O.	F	14	Giant cell tumor left tibia	4180 r 18 mos. 2840 r	Regenerative capacity of bone apparently completely lost at amputation 10 mos. after last treatment
19	L. L.	M	13	Endothelial myeloma right humerus	6025 #	Regenerative capacity slightly impaired 9 yrs.
20	M. G.	F	10	Endothelial myeloma left tibia	5450 # 22 mos. 2875 r	Mineralization of bone not involved by tumor impaired following first treatment & further impaired following second treatment
21	J. A.	M	28	Giant cell tumor left ilium	2685 r 3 mos. 2360 r 2 mos. 2750 #	2nd & 3rd courses, 1000 Kv. radiation. Regenerative capacity of bone almost completely destroyed 2½ yrs. after last treatment
22	M. W.	M	18 mos.	Endothelial myeloma right clavicle	3580 r 6 mos. 2340 r	Bone growth retarded 3 yrs. after last treatment; retardation continued 9 yrs. Mineralization not impaired

doses on bone regeneration in patients comparable in age and in location of lesions.

It is well known that irradiation of the epiphyseal regions in young animals will inhibit bone growth. Doses as small as 600 r have been reported to cause temporary reduction in growth-rate and large doses will stop growth permanently. In our young patients we found the expected retardation of growth in irradiated bones. Despite the fact that young bone does not grow normally after irradiation, it is evident that its regenerative capacity is much more resistant to radiation injury than is that of adult bone. Cases 14, 15, 19, and 22 tolerated bone doses in excess of 5000 r without severe damage. That such large doses are by no means safe even in young bone is shown by the bad results obtained in Cases 18 and 20.

In summary, it appears that, in the adult, radiation therapy involving the delivery of doses in excess of 3000 r to bone should not be used for benign lesions because of the danger of damage to the regenerative capacity of the bone. For malignant lesions, bone doses up to 4000 r may be used in the expectation that the bone, although permanently damaged, will retain a considerable degree of useful function. Radiation doses much higher than this may be expected to cause such severe damage that the final results will range from the unsatisfactory to the disastrous.

In children, radiation of bone for benign lesions, such as bone cyst, should be administered with extreme caution or not at all because of the danger of causing crippling or disfiguring retardation of growth. This unfortunate sequel has been observed on numerous occasions. For malignant lesions, where limitation of growth is of secondary importance, bone doses as high as 5000 r may usually be given with a fair prospect of preservation of useful function should the patient be fortunate enough to survive. This is not to be construed as indicating that radiation is preferable to radical surgery for operable lesions.

EFFECT OF RADIATION ON OSTEOGENIC SARCOMA

Table XLIV shows the effect of radiation on 39 cases of osteogenic sarcoma. In all except Case 10 the diagnosis was confirmed histologically, following either biopsy or radical surgery. The effects of radiation were evaluated on the basis of clinical improvement, reduction in serum or tissue alkaline phosphatase, and histologic evidence of damage to tumor tissue. The effects of various tumor doses are summarized in Table XLV.

The clinical effect consisted in relief of pain, reduction in swelling, and improvement in general physical status. In those patients who underwent amputation immediately after the completion of irradiation there was usually not sufficient interval of time to permit an evaluation of the clinical

effect; however in a few instances very prompt relief was noted as shown in the table.

When the serum alkaline phosphatase was elevated prior to treatment, a subsequent fall during treatment, or low phosphatase readings in the tumor tissue obtained after treatment indicated that the rate of growth of the tumor had been reduced. Some types of osteogenic sarcoma do not produce excess phosphatase. In such cases the phosphatase readings could not be used as an index of rate of growth; they are omitted from the table.

When the patient submitted to amputation within a few weeks after completion of irradiation, the pathologist's report indicated the extent of damage to the tumor. We are indebted to Dr. F. W. Stewart for reviewing the microscopic sections of many of these cases. When, as in Cases 18, 24, and 28, there was initial clinical relief followed several months later by relapse and amputation, the histologic findings are omitted, since most of the tumor tissue obtained at such late operation had been formed after the effect of irradiation had disappeared. Some patients, i.e., Cases 7, 8, 10, 22, 30, and 34, had no radical surgery and no tissue was available for evaluating radiation effect.

Of the patients included in the table, 8 received tumor doses of less than 3000 r. Transitory and incomplete control of disease was obtained in 2 cases. In the remaining 6 there was no demonstrable effect beyond some diminution in phosphatase activity. It appears that doses as small as these are of little use.

Eight patients received tumor doses between 3000 r and 4000 r. There was some evidence of control of disease in all cases. Clinical control was transitory, and tumor-tissue damage, while marked in 2 cases, was not sufficient to devitalize the tumor.

Sixteen patients received tumor doses between 4000 r and 6000 r. Marked clinical control of disease and marked tumor tissue damage were obtained regularly, but there was no evidence that permanent control had been obtained.

Eight patients received tumor doses between 6000 r and 9000 r. There was evidence of marked control of disease in all cases and in 2 the tumor appeared to have been completely destroyed.

In general, it appears that tumor doses of less than 4000 r produce only transitory and irregular control of osteogenic sarcoma. Doses larger than 4000 r can usually be relied upon to control the disease locally for a number of months but it is only with doses of the order of 8000 r that there is evidence that an occasional tumor can be devitalized permanently. Since it is frequently difficult or impossible to deliver to the tumor doses much in excess of 3000 r without causing irreparable damage to the adjacent normal structures, it is evident that radiation therapy affords little hope of permanent control of osteogenic sarcoma. It is, however, a useful palliative

TABLE XLIV
EFFECT OF RADIATION ON OSTEOGENIC SARCOMA*

CASE NO.	NAME	AGE	SEX	DIAGNOSIS	DOSE TO TUMOR	CLINICAL	EFFECT OF RADIATION PHOSPHATASE	MICROSCOPIC	REMARKS
1	H. D.	20	F.	Osteogenic sarcoma left lower femur	850 r		No effect	No effect	Amputation 7 days after end of treatment
2	S. L.	44	F.	Sclerosing osteogenic sarcoma, left lower femur	1350 r		No effect	No effect	Amputation 4 days after end of treatment
3	L. H.	20	M.	Telangiectatic & osteoblastic osteogenic sarcoma, right fibula	1360 r		Slight inactivation	No effect	Amputation 5 days after end of treatment
4	A. C.	19	F.	Medullary spindle cell sarcoma, right lower femur	1600 r		Marked inactivation	No effect	Amputation 3 days after end of treatment
5	M. L.	11	F.	Periosteal and medullary spindle cell osteogenic sarcoma, left lower element femur	2000 r Radium pack	Relief for 3 mos. then relapse	Inactivation for 3 mos.		Amputation 3 mos. after end of treatment
6	L. H.	18	M.	Telangiectatic osteogenic sarcoma	2100 r			No effect	Amputation 5 days after end of treatment
7	W. J.	16	M.	Osteogenic sarcoma left upper humerus	2485 r	Slight transitory relief	Partial inactivation		Patient refused operation & died 5 mos. after end of treatment
8	M. L.	54	F.	Osteogenic sarcoma left lower femur	2550 r	No effect	No effect		Patient inoperable because of metastases. Died 5 mos. after end of treatment
9	J. S.	12	M.	Telangiectatic osteogenic sarcoma left lower femur	3000 r		Partial inactivation	No effect	Amputation 5 days after end of treatment
10	A. W.	4½	F.	Roentgen diagnosis of osteogenic sarcoma, left lower femur	3040 r	Relief for 2 mos. then relapse			
11	R. S.	6	M.	Osteogenic sarcoma, left lower femur	3160 r	Relief for 2 mos. then relapse	No effect	No effect	Amputation 2½ mos. after end of treatment
12	W. R.	23	M.	Large spindle cell and giant cell osteogenic sarcoma with osteoid and cartilage production, left lower femur	2700 r 4 mos. 1000 r	Partial relief 4 mos. None	Serum phosphatase rose during treatment	No effect	Original diagnosis was giant cell tumor. Amputation 1 mo. after last treatment showed osteogenic sarcoma unaffected by radiation
13	H. G.	13	M.	Osteogenic sarcoma, left lower femur	3300 r	Relief until amputation, 2 wks	Almost complete inactivation	No effect	Amputation 2 wks. after end of treatment
14	J. C.	16	M.	Large spindle cell and giant cell osteogenic sarcoma, left upper humerus	3700 r plus P ₂₅		Marked inactivation	Considerable necrosis, but tumor still viable	Patient received enough radioactive phosphorus to give 200 to 300 r to the tumor

15	B H	17	M.	Osteogenic sarcoma, right lower femur	3775 r		Marked inactivation	Marked inactivation	Amputation 5 days after end of treatment
16	M A.	11	F.	Osteogenic sarcoma, right lower femur	3920 r at 1000 Kv.	Partial relief until amputation, 2 wks.		Marked inactivation	Amputation 2 wks. after end of treatment
17	M. R.	15	M.	Periosteal & medullary osteogenic sarcoma, right lower femur	4000 r	Partial relief until amputation, 3 wks.	Marked inactivation	Almost completely destroyed	
18	D. L	7	F.	Osteogenic sarcoma, right lower femur	4000 r	Marked relief 6 mos. then relapse	Marked inactivation		Patient lost to follow-up for 9 mos., then reappeared with huge recurrence & submitted to amputation. No tissue was available immediately after irradiation for study of effect of treatment
19	S. G.	16	M.	Osteogenic sarcoma, partially sclerosing, partly small spindle cell, left lower femur	4100 r		Marked inactivation	No conspicuous changes	Amputation 4 days after end of treatment
20	H. G	17	M.	Osteogenic sarcoma, right lower femur	4200 r	Partial relief 1 mo. then relapse	Slight inactivation	No effect	Amputation 1 mo. after end of treatment
21	G. D.	11	F.	Osteogenic sarcoma, right lower femur	4300 r			Marked inactivation	Amputation 4 days after end of treatment
22	J F.	15	M.	Osteogenic sarcoma, right upper femur	4320 r	Marked relief 5 mos. then relapse			Patient refused amputation and died 9 mos. after end of treatment
23	V. H.	13	F.	Osteogenic sarcoma, right lower femur	4340 r	Partial relief until amp., 1 mo.		Slightly infarcted but fully viable	Amputation 1 mo. after treatment
24	A V.	22	M	Osteogenic chondrosarcoma, right upper humerus	4550 r	Marked relief 3 yrs. then relapse			Amputation 2 yrs. after end of treatment. No tissue was available immediately after irradiation for study of effect of treatment
25	G. S.	16	M.	Osteogenic sarcoma, right lower femur	4600 r		None	Slight changes but fully viable	Amputation 5 days after end of treatment
26	H H.	6	M.	Osteogenic sarcoma, right upper humerus	4695 r	Marked relief until amputation 5 wks.	Marked inactivation	Infarcted but fully viable	Amputation 5 wks. after end of treatment
27	A C	20	M	Low-grade chondrosarcoma left radius	2250 r 6 mos. 3600 r	Growth of tumor probably retarded	None	Partial inactivation	Amputation 9 mos. after end of second course of treatment

TABLE XLIV (CONTINUED)

CASE No.	NAME	AGE	SEX	DIAGNOSIS	DOSE TO TUMOR	CLINICAL	EFFECT OF RADIATION PHOSPHATASE	MICROSCOPIC	REMARKS
28	W. K.	28	M.	Osteogenic sarcoma, right tibia	4750 r	Marked relief 10 mos. then relapse	Marked inactivation		Amputation 17 mos. after end of treatment. No tissue was available immediately after irradiation for study of effect of treatment
29	J. K.	24	M.	Large polyhedral cell osteogenic sarcoma, left lower femur	4835 r	Relief 2 mos., then relapse		Partial inactivation	Amputation 3 mos. after end of treatment
30	D. C.	17	F.	Osteogenic sarcoma, right lower femur	5200 r	Marked relief 2 mos. then relapse	Marked inactivation		Patient refused amputation
31	S. R.	11	M.	Osteogenic sarcoma, left upper humerus	5300 r	Little change	Some inactivation	Marked inactivation but still viable	Amputation 9 days after end of treatment
32	S. B.	11	M.	Osteogenic sarcoma, right upper humerus	5750 r		Some inactivation	No effect	Amputation 1 mo. after end of treatment
33	A. C.	14	M.	Osteogenic sarcoma, right lower femur	6445 r	Little change		Almost complete destruction	Amputation 1 week after end of treatment
34	A. N.	11	F.	Low-grade chondromyxosarcoma, left tibia	6575 r	Marked relief 18 mos.			Amputation 1 week after end of treatment Patient died of lung metastases 18 mos. after end of treatment without evidence of recurrence of primary
35	S. S.	16	F.	Osteogenic sarcoma, left upper humerus	6800 r		Marked inactivation	Almost complete destruction	Amputation 1 wk. after end of treatment
36	E. C.	14	F.	Osteogenic sarcoma, left lower femur	5580 r 11 mos. 3520 r at 1000 Kv. p ²⁷	Clinical relief of primary until death from lung metastases	Marked inactivation	Small nests of questionably viable cells found at autopsy	Amputation refused and patient died of lung metastases 7 mos. after end of treatment without evidence of recurrence of primary
37	W. K.	12	M.	Osteogenic sarcoma, right lower femur	8000 r		Marked inactivation	Apparent complete destruction	Amputation 2 wks. after end of treatment
38	R. H.	14	M.	Osteogenic sarcoma, left lower femur	8000 r	Partial relief until amputation, 11 wks.	Probably some inactivation	Definitely inactivated but viable	Amputation 3 wks. after end of treatment
39	A. M.	7	F.	Osteogenic sarcoma, left lower femur	9000 r	Moderate relief until amputation, 11 wks.	Marked inactivation	Partly inactivated but viable	Amputation 3 wks. after end of treatment

* Diagnoses verified histologically unless otherwise noted. Radiation used—700–250 Kv. Roentgen rays unless otherwise noted.

TABLE XLV
OSTEOGENIC SARCOMA: EFFECT OF VARIOUS TUMOR DOSES

TUMOR DOSE	NUMBER OF CASES	CLINICAL EFFECT	EFFECT ON PHOSPHATASE ACTIVITY	HISTOLOGIC EFFECT
Less than 3000 r	8	Little or none	Some decrease	None
3000 r to 4000 r	8	Transitory control in some cases	Some decrease	None
4000 r to 6000 r	16	Control for several months in most cases	Decrease in all cases	Varying degrees of devitalization but none complete
6000 r to 9000 r	7	Marked clinical control in all cases—occasional complete inactivation	Complete inactivation in all cases	Severe damage in all, and tumor appeared not viable in 2 cases

agent for patients with inoperable disease or those who refuse radical surgery.

In a series of 67 five-year survivals of osteogenic sarcoma reported from the Bone Sarcoma Registry by Crowell in 1935 there were 8 cases in which amputation was not performed; in 5 of these radium was used in connection with local excision; there was only 1 in which the tumor was treated by roentgen-rays alone.

ENDOTHELIOMA OF BONE

It is difficult to judge the ultimate effect of radiation therapy on endothelioma of bone because the disease is so malignant that most patients die of disseminated metastases before the final effect of treatment of the primary lesion is apparent. In the accompanying table (p. 554) the effect of radiation on the primary tumor was evaluated in 3 patients by the microscopic appearance of tissue removed surgically soon after treatment. In 10 cases the effect of radiation was evaluated by clinical observation for a period of from one to eleven years.

The results shown in the table suggest that endothelioma of bone is quite variable in its response to irradiation. Thus, in Cases 4, 5, 6, and 8 good results were obtained in the primary tumor with tumor doses of from 3720 r to 4550 r, and in Case 3 with only 3240 r. On the other hand, Cases 7 and 9 showed only temporary control of the primary tumor after similar doses. Doses greater than 5000 r controlled the primary tumor in Cases 10 to 12 inclusive for periods up to nine years. In Cases 10 and 12 there was severe damage to adjacent normal structures but in Case 11 the final result was very satisfactory.

RETICULUM CELL SARCOMA OF BONE

A sufficiently wide experience in the treatment of primary reticulum cell sarcoma of bone by roentgen therapy has not yet accumulated to enable us to present our conclusions statistically. We believe however that

NEOPLASMS OF BONE

TABLE XLVI
EFFECT OF RADIATION ON ENDOTHELIOMA OF BONE*

NAME	SEX	AGE	DIAGNOSIS	DOSE IN ROENTGENS TO TUMOR	EFFECT
F. K.	F	7	Endothelioma fibula	1380 14 mos. 350	Regression followed by recurrence after 14 mos. Little change for 9 mos., then local recurrence and distant metastases
T. B.	M	■	Endothelioma left tibia	3185	Tumor fully viable at amputation 1 wk. after end of treatment. Patient died of generalized metastases 5½ yrs later
W. L.	M	32	Atypical endothelioma right upper femur	3240	Regression of primary tumor without recurrence until death from metastases 18 mos. after end of treatment
A. M.	M	27	Endothelioma left femur	3720	Regression of primary tumor without recurrence until death from metastases 13 mos after end of treatment
D. L.	M	14	Endothelioma right fibula	3960 1970	No evidence residual tumor at resection 2 mos. after end of treatment Treatment of lung metastasis caused complete regression followed in 3 mos. by recurrence & death
W. B.	M	14	Endothelioma right fibula; slightly atypical	4000	No evidence residual tumor at resection 6 wks. after end of treatment. Patient free of disease 6 yrs
W. V.	M	30	Endothelial myeloma right femur	4185 4 mos. 585	Tumor controlled for 17 mos. after first treatment, then recurred & was amputated. Pt. died of metastases 30 mos. after beginning of treatment
M. J.	M	6	Endothelioma right radius	4550	Regression of primary tumor without recurrence
R. H.	F	12	Malignant tumor consistent with endothelioma of bone—right fibula	4740 11 mos. 1745	Regression of primary tumor without recurrence & was given further treatment Pt. died of metastases 17 mos after first treatment without further activity of primary
M. G.	F	10	Endothelioma left tibia	5450	Regression of primary tumor without recurrence 2 yrs. Marked fibrosis & contracture
L. L.	M	13	Endothelioma right humerus	6025	Patient free of disease 9 yrs. after treatment. Good function with slight muscle atrophy & slight demineralization
E. L.	F	18	Endothelioma right tibia	6300	No recurrence of primary 15 mos but extreme fibrosis & threatened skin ulceration. Generalized metastases

* Diagnosis verified by microscopic examination in all cases

the following observations are justified. This tumor is definitely radiosensitive. It responds in much the same striking manner as is generally seen in Ewing's sarcoma but it seems probable that it requires for lasting inactivation a total depth dose that is considerably below that which we believe is necessary for complete control in the latter tumor. We have treated a case with as small a depth dose as 2200 r and obtained an eight-year survival without evidence of the disease. In another case which received 1700 r in a course completed two weeks prior to amputation, Dr. Stewart found no viable tumor cells in the operative specimen.

While these doses seem very small for the control of a malignant bone neoplasm, it would appear that tumor doses of the order of 2500 r may be sufficient to produce permanent inactivation of reticulum cell sarcoma

of bone. Doses of this magnitude are not likely to produce serious damage to the adjacent normal bone. Radiation therapy appears to be the method of choice in reticulum cell sarcoma of bone.

GIANT CELL TUMOR

Our series of giant cell tumors treated by radiation is too small and the methods of treatment employed are too varied for a detailed evaluation. Three patients received tumor doses ranging from 925 r to 1200 r with control of the tumor and good bone regeneration over a period of from one to four years. After four years the tumor which received 1200 r recurred and was given a tumor dose of 1120 r. There has been no further evidence of activity in the succeeding five years. The other 2 cases have been observed for only about one year and may still show late recurrence. It is probable that doses as small as 1000 r will give permanent control in only an occasional giant cell tumor.

Four patients received tumor doses ranging from 1950 r to 3800 r in one, two, or three cycles. They have shown no recurrence of the tumor and have had good functional results over a period of from one to fourteen years. The patient who received the largest dose exhibits some impairment in bone regeneration and marked skin damage with ulceration beginning twelve years after treatment. It seems likely that doses ranging from 2000 r to 3000 r will control most giant cell tumors.

Four patients received tumor doses of 3600 r to 7800 r in one, two, or three cycles. There was no recurrence of the tumor over a period of from one to three years, but late radiation changes in the skin and bone made the end results highly unsatisfactory. The effect of large doses of radiation on bone regeneration is discussed more fully elsewhere, but it is noteworthy that the reason for administering further radiation cycles to two of these patients was failure in recalcification after initial tumor doses of about 2700 r. This was erroneously interpreted as indicating residual activity of the tumor, but subsequent study strongly suggests that the effect was really an impairment of the regenerative capacity of the adjacent normal bone.

Before deciding upon irradiation as the method of choice in the treatment of a giant cell tumor the following questions must be answered: Is the area involved readily accessible for surgical treatment? If so, can a better permanent functional result be obtained by operation or by irradiation? If one decides in favor of irradiation, then the method of administration must be planned. It is probably wiser to deliver the total proposed dosage in a single course of treatment rather than to carry out successive courses at intervals. From the foregoing analysis of cases treated by roentgen therapy it appears unwise to expect control from doses as low as 1000 r, and it is certainly inadvisable to give more than 3000 r because of the

NEOPLASMS OF BONE

TABLE XLVI
EFFECT OF RADIATION ON ENDOTHELIOMA OF BONE*

NAME	SEX	AGE	DIAGNOSIS	DOSE IN ROENTGENS TO TUMOR	EFFECT
F. K.	F	7	Endothelioma fibula	1380 14 mos 350	Regression followed by recurrence after 14 mos. Little change for 9 mos., then local recurrence and distant metastases
T. B.	M	8	Endothelioma left tibia	3185	Tumor fully viable at amputation 1 wk. after end of treatment. Patient died of generalized metastases 5½ yrs. later
W. L.	M	32	Atypical endothelioma right upper femur	3240	Regression of primary tumor without recurrence until death from metastases 18 mos after end of treatment
A. M.	M	27	Endothelioma left femur	3720	Regression of primary tumor without recurrence until death from metastases 13 mos. after end of treatment
D. L.	M	14	Endothelioma right fibula	3960 1970	No evidence residual tumor at resection 2 mos. after end of treatment Treatment of lung metastasis caused complete regression followed in 3 mos. by recurrence & death
W. B.	M	14	Endothelioma right fibula; slightly atypical	4000	No evidence residual tumor at resection 6 wks. after end of treatment. Patient free of disease 6 yrs.
W. V.	M	30	Endothelial myeloma right femur	4185 4 mos. 585	Tumor controlled for 17 mos. after first treatment, then recurred & was amputated. Pt. died of metastases 30 mos after beginning of treatment
M. J.	M	6	Endothelioma right radius	4550	" " "
R. H.	F	12	Malignant tumor consistent with endothelioma of bone—right fibula	4740 11 mos 1745	curred & was given further treatment Pt. died of metastases 17 mos after first treatment without further activity of primary
M. G.	F	10	Endothelioma left tibia	5450	Regression of primary tumor without recurrence 2 yrs. Marked fibrosis & contracture
L. L.	M	13	Endothelioma right humerus	6025	Patient free of disease 9 yrs after treatment. Good function with slight muscle atrophy & slight demineralization
E. L.	F	18	Endothelioma right tibia	6300	No recurrence of primary 15 mos. but extreme fibrosis & threatened skin ulceration Generalized metastases

• Diagnosis verified by microscopic examination in all cases

the following observations are justified. This tumor is definitely radiosensitive. It responds in much the same striking manner as is generally seen in Ewing's sarcoma but it seems probable that it requires for lasting inactivation a total depth dose that is considerably below that which we believe is necessary for complete control in the latter tumor. We have treated a case with as small a depth dose as 2200 r and obtained an eight-year survival without evidence of the disease. In another case which received 1700 r in a course completed two weeks prior to amputation, Dr. Stewart found no viable tumor cells in the operative specimen.

While these doses seem very small for the control of a malignant bone neoplasm, it would appear that tumor doses of the order of 2500 r may be sufficient to produce permanent inactivation of reticulum cell sarcoma

of bone. Doses of this magnitude are not likely to produce serious damage to the adjacent normal bone. Radiation therapy appears to be the method of choice in reticulum cell sarcoma of bone.

GIANT CELL TUMOR

Our series of giant cell tumors treated by radiation is too small and the methods of treatment employed are too varied for a detailed evaluation. Three patients received tumor doses ranging from 925 r to 1200 r with control of the tumor and good bone regeneration over a period of from one to four years. After four years the tumor which received 1200 r recurred and was given a tumor dose of 1120 r. There has been no further evidence of activity in the succeeding five years. The other 2 cases have been observed for only about one year and may still show late recurrence. It is probable that doses as small as 1000 r will give permanent control in only an occasional giant cell tumor.

Four patients received tumor doses ranging from 1950 r to 3800 r in one, two, or three cycles. They have shown no recurrence of the tumor and have had good functional results over a period of from one to fourteen years. The patient who received the largest dose exhibits some impairment in bone regeneration and marked skin damage with ulceration beginning twelve years after treatment. It seems likely that doses ranging from 2000 r to 3000 r will control most giant cell tumors.

Four patients received tumor doses of 3600 r to 7800 r in one, two, or three cycles. There was no recurrence of the tumor over a period of from one to three years, but late radiation changes in the skin and bone made the end results highly unsatisfactory. The effect of large doses of radiation on bone regeneration is discussed more fully elsewhere, but it is noteworthy that the reason for administering further radiation cycles to two of these patients was failure in recalcification after initial tumor doses of about 2700 r. This was erroneously interpreted as indicating residual activity of the tumor, but subsequent study strongly suggests that the effect was really an impairment of the regenerative capacity of the adjacent normal bone.

Before deciding upon irradiation as the method of choice in the treatment of a giant cell tumor the following questions must be answered: Is the area involved readily accessible for surgical treatment? If so, can a better permanent functional result be obtained by operation or by irradiation? If one decides in favor of irradiation, then the method of administration must be planned. It is probably wiser to deliver the total proposed dosage in a single course of treatment rather than to carry out successive courses at intervals. From the foregoing analysis of cases treated by roentgen therapy it appears unwise to expect control from doses as low as 1000 r, and it is certainly inadvisable to give more than 3000 r because of the

danger of causing irrevocable damage to the skin, soft tissues, joint cartilage, and bone.

The treatment of giant cell tumor by roentgen rays predicates a cessation of tumor growth followed by regeneration of bone in the tumor-bearing area. It is futile to irradiate with a dose which, although it may be adequate to control the tumor, is so great that it prevents restoration of continuity of the destroyed area by bone repair. In the past some cases received excessive radiation and the ultimate damage was sufficient to require amputation.

It has never before been shown convincingly just what dosage will control a giant cell tumor permanently and at the same time spare the capacity of normal bone to regenerate and restore the involved area. Our experience leads to the assumption that this theoretical ideal dose is not dependent upon the radiosensitivity of the component cells of the giant cell tumor. It depends rather upon the radiation required to interrupt the aneurysmal-like pulsations of the vessels within the tumor which cause the progressive erosion of the cancellous bone, while permitting the restoration of the destroyed area by sparing the regenerative capacity of the adjacent bone.

For the average giant cell tumor situated in an accessible location, surgery is the preferred method of treatment. Naturally, for those that are inaccessible, irradiation is generally advisable. In the average case a dose of from 1500 r to 1800 r delivered to the tumor should be both sufficient and safe. Larger doses must be regarded as questionable; they should seldom reach as high as 3000 r. Wherever possible two or more portals should be used, proper protection being afforded the adjacent joint. The smallest portal that covers the involved area should be chosen since it is unnecessary to expose bone beyond that portion which is revealed by roentgenograms to be involved. Due care should be exercised to avoid overlapping of the fields.

Following irradiation the same care to prevent pathological fracture should be taken as is observed in surgical cases. Proper protection should be afforded until the repair is adequate to insure against fracture or collapse of the tumor-bearing area. In the lower extremity the danger of unprotected weight-bearing resulting in partial collapse justifies the routine use of caliper splints, crutches, and plaster casts. For the upper extremity, joint function can be attained more readily by the use of removable splints or a sling.

57. EFFECT OF RADIUM POISONING ON SKELETAL TISSUES

MARTLAND HAS MADE NOTABLE CONTRIBUTIONS TO OUR KNOWLEDGE OF the effect of ingested or inhaled radioactive substances upon the body, and the eventual fate of the individual when the bone marrow and hemopoietic system is seriously damaged. His interest was attracted to this subject when he became involved in a study of a group of radium-dial painters who continuously ingested small amounts of radioactive substance over long periods. He found that most of these substances are eliminated through the intestinal tract but that the part not excreted is stored in the liver, spleen, and bones (reticuloendothelial system) as carbonates, phosphates, and sulphates, and that the toxic effect of radium deposits in bone is due wholly to the radiation, of which 92 per cent is from alpha rays, a negligible amount from beta and gamma rays.

The effect of the alpha particles is highly disruptive, causing disintegration of molecules within the tissues. Gradually this irritating stimulus results in a hyperplastic bone marrow. Megaloplastic erythropoiesis is prominent. The blood picture may resemble the anemia of Addison's disease. The granulocytes, with the exception of eosinophiles, are reduced in numbers so that an agranulocytic syndrome is often seen. This constitutes the first phase of radiation osteitis.

The second phase, appearing after a period of months or years, is characterized by a patchy subsidence of the process followed by a highly inflammatory and cellular replacement fibrosis in which plasma cells, lymphocytes, and myelocytes abound. Many of these fibroblasts reveal hyperchromatic nuclei, and mitoses are frequent. Such areas closely resemble sarcoma, and it is here that Martland believes that sarcoma undoubtedly arises.

The third and final stage—that of healing—is marked by a subsidence of the inflammatory activity, a replacement of the marrow by acellular fibrous tissue, and a softening of the bones due to partial decalcification. Pathologic fractures may then occur.

The degree of symptoms and the interval between exposure and exten-

danger of causing irrevocable damage to the skin, soft tissues, joint cartilage, and bone.

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The degree of symptoms and the interval between exposure and exten-

sive radiation osteitis depend upon the amount of radioactive substance retained in the body. Martland states that 120 to 180 mg. will, within one to five years, bring about marked radiation osteitis widely distributed throughout the skeleton. Definite destruction of bone has occurred, however, where as little as 0.5 mg. were contained in the entire body.

Since in cases of long standing the skeleton accounts for 98 per cent of the deposition, it is readily understood why the development of a primary malignant bone sarcoma is so regularly induced. The interval between the causation of exposure and development of sarcoma is given by Martland as from eight to ten years; in experimental rats the period is upward of π year.

It should be emphasized that the effects of radium on bone just described are not due to a chemical poison. The amounts of radium absorbed, only a few micrograms, are too small to cause chemical effects even if radium were a highly toxic metal, which it probably is not. The effects are due to irradiation delivered within the bone substance over a period of years.

The recent production of large numbers of radioactive isotopes by atomic fission makes it likely that the induction of bone tumors by absorbed radioactive material will constitute an important health hazard in the future. At the present time the results of many studies in this field are still subject to security restrictions but the following highly significant observations on the effects of radioactive strontium and plutonium have been made public.

Strontium is an element which resembles calcium metabolically. It deposits selectively in bone and is toxic only in massive doses. The naturally occurring element is not radioactive. Two radioactive isotopes have been made, of which the more abundant has a half life of fifty-three days. When this isotope was administered to mice in doses insufficient to cause immediate toxic effects, bone tumors appeared ultimately in 80 per cent of the animals. The majority of the tumors were osteogenic sarcomas, although some fibrosarcomas were also seen. The production of these tumors is probably closely analogous to the production of osteogenic sarcomas in the radium-dial workers.

Plutonium is a highly toxic radioactive element which is deposited in various parts of the body. In large doses it acts both as a chemical and as a radioactive poison and causes death too promptly for effects on the bones to become apparent. In doses too small to be fatal immediately it is deposited in the organic matrix of the bone, especially along the periosteum and endosteum. In the experimental animals which survive long enough, malignant bone tumors appear.

In the examples just cited the appearance of malignant change in bone rather than in other organs is not due to any specific sensitivity of this tissue but rather to the concentration of radioactive material in the bone substance. The chemical properties of the radioactive elements are im-

portant only as they determine in which tissue they will be deposited. As the use of radioactive isotopes in medicine becomes more common, and as large numbers of industrial workers are exposed to the danger of absorption of these materials, it will become increasingly important to guard against the deposition of long-lived radioactive materials in tissues, such as bone, which have a very slow turnover of their constituent elements.

TYPE OF BONE SARCOMA INDUCED BY RADIUM POISONING

These tumors have the characteristics of spontaneous osteogenic sarcoma. Commencing in the spongiosa and extending through the cortex and even though the periosteum they present as an extrasosseous mass. Although capable of bone formation they resemble the highly anaplastic and rapidly growing sarcomas in that they produce mainly osteolytic changes. The symptoms are those that are common to the ordinary osteogenic sarcoma. Pathologic fracture may occur and is made more probable by the brittleness of bone induced by the prolonged effect of radiation on bone cells.

The diagnosis rests upon the demonstration that a malignant bone tumor exists in a patient who is known to have been in contact with radioactive substances which could have been ingested or inhaled and in whom radioactivity is shown to be present.

TREATMENT

The therapy is surgical and does not differ from that applicable to any other osteogenic sarcoma. Martland has noted the fact that radium sarcomas are not likely to metastasize early. Where no evidence of pulmonary involvement exists an amputation, if feasible, should be seriously considered.

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SECTION NINE

Constitutional Therapy

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58. EFFECTS OF BACTERIAL PRODUCTS ON TUMORS OF BONE

FOR THE PAST THREE HUNDRED YEARS IT HAS BEEN KNOWN THAT CERTAIN acute bacterial infections, notably erysipelas, have occasionally produced a dramatic clinical regression in human cancer. In some instances there was complete regression; the patients were followed for a considerable period. Busch was apparently the first to publish detailed observations of this phenomenon in 1866. During the next twenty-five years cases were also reported by a number of other physicians including Dauchez, Mosengeil, Gillette, Bruns, Pamard, Stein, Mishtolt, Richochon, Biedert, Plenio, Wyeth, Barton, Kutzner, Czerny, and Kleeblatt.

As to the effects produced by this beneficial action of erysipelas on neoplasms, Delbet stated that at first there is a more or less pronounced swelling and softening of the tumors, followed by regression. In some the rate of diminution is surprisingly rapid while in others extremely slow. The beneficial effects were at first attributed to a direct bacterial antagonism. The observations of Janicke and Neeser, and Feilchenfeld, appeared to favor this view. It was found, however, that erysipelas developing at a distance from the growth occasionally also produced the same salutary effect. It appeared, therefore, that there was a general as well as a local action. Bruns attributed the beneficial effects of infectious diseases on neoplasms to the unusually high fever. In the same manner Delbet states that Mosetig Moorhof regarded the result as due to the exaggerated metabolism caused by the fever.

The mechanism by which these striking effects are produced is still not clearly understood but in recent years Shwartzman, Shear, Duran-Reynals, and other investigators have shown beyond question that certain preparations of bacterial toxins will, when injected into tumor-bearing animals, produce hemorrhage, edema, and at times actual necrosis in the tumors. This action is highly selective, takes place within two to four hours and is

confined almost without exception to the tumor, leaving normal tissues unaffected.

COLEY'S MIXED TOXINS

Busch was the first to attempt to produce an attack of erysipelas in a patient suffering from a malignant tumor. (This was in 1868, or thirteen years before the discovery of the streptococcus of erysipelas.) The skin over the extensive inoperable tumor, a lymphosarcoma of the neck, was lightly cauterized, and the patient was then placed in a bed notorious for the frequency with which patients in it were attacked with erysipelas. The desired result took place four days later and the growth disappeared rapidly in all but a small portion, which, however, again became enlarged. The result was, therefore, only a partial one but it encouraged further trials.

As soon as the streptococcus of erysipelas was discovered by Fehleisen in 1881, the accidental results which had been reported by various physicians suggested the advisability of inoculating living cultures of erysipelas in cases of malignant tumors, as a therapeutic measure. Fehleisen was the first to inoculate human patients with living cultures of *Streptococcus erysipelatis*, in 1882. The same year Winslow also made the attempt, followed by Holst in 1888, and Kleeblatt in 1890.

These experiments were unknown to the late William B. Coley when his interest in this phenomenon was first aroused by a case of thrice-recurrent inoperable lymphosarcoma of the neck that had recovered under an accidentally contracted erysipelas infection at the New York Hospital in 1884, and was free of disease in February 1891, when he first heard of the patient. This observation prompted Coley to make an extensive survey of the literature and he found records of 38 cases of inoperable malignant tumors in which an attack of erysipelas had occurred either by accident or inoculation. Many of these patients showed marked improvement, and in others the tumor completely disappeared but later recurred. In 10 of the 38 cases the regression and final disappearance of the tumor was not followed by a recurrence.

Beginning in April, 1891, Coley attempted to produce erysipelas as a therapeutic measure in 10 cases of inoperable malignant tumors. The difficulty of producing an attack and the dangers incident to inoculations with living cultures prompted him to try killed cultures sterilized by heating (at first to 100° C., later to 58° C.) or by filtration, but these three preparations were too weak to be effective.

In December, 1892, Coley learned of the investigation of Roger at the Pasteur Institute on the effects of *Bacillus prodigiosus* (*Serratia marcescens*) when associated with other organisms. These experiments suggested that *Bacillus prodigiosus* or its toxins may increase the virulence of

other organisms with which they are associated in their proliferating stage. For this reason, the toxins of *B. prodigiosus* were incorporated in the formula which became known as *Coley's Mixed Toxins*. Research by Beebe and Tracy in 1906, and later by Schwartzman, have clearly indicated that the toxins of *B. prodigiosus* appear to possess higher titers of tumor-hemorrhage producing toxins than do most strains of *streptococcus*.

At least fifteen different preparations of *Coley's Toxins* have been used since *Coley's* first experiments in 1892, of which three were apparently more potent than the rest. Since December 1899, Parke, Davis and Company have prepared the toxins. Since 1921 their preparation has been the only one available in the United States. Unfortunately it appears to have been weak. Their research laboratories are now cooperating in attempts to improve the effectiveness of the product. In 1946, Stock, of Memorial Hospital, prepared a modified formula of *Coley's Mixed Toxins*, using fresh cultures of both organisms. This formula is at present (1948) being subjected to clinical trial.

One of the most persistent experimental studies in this field has been made by Shear, who has isolated an active fraction, apparently a polysaccharide from the toxins of *B. prodigiosus* (*Serratia marcescens*) which, according to his tests, was 1300 times more potent as regards the tumor-hemorrhage factor than the commercial product available in 1943. In 1944 The Lankenau Hospital Research Institute in Philadelphia began a study of the effects of Shear's polysaccharide upon human neoplasms, a significant feature of which was serial biopsies before and during treatment. These studies appear to indicate that the tumor cell is most vulnerable to the bacterial products during mitosis, particularly the metaphase; the unusual histologic changes produced under treatment were clearly shown by the cytologic studies of Irene G. Diller. This work suggests that anything which inhibits the rate of mitosis during toxin therapy may also slow up the destruction of the tumor cells by these agents.

During the past half century there have been numerous reports from investigators here and abroad expressing favorable or unfavorable opinions as to the efficacy of the method. For a comprehensive analysis of this material the reader is referred to the review of Nauts, Swift, and *Coley*.

Our experience with *Coley's Mixed Toxins* is limited almost exclusively to the preparation made by Parke, Davis and Company since 1921. It has been our impression that this preparation has been weak in its effect upon bone tumors as well as upon other malignant neoplasms. Although we have used it rather extensively over this twenty-five-year-period, it is difficult to determine what part it has played in the survival of the cases that have lived for prolonged periods following its administration, since most of the cases were also treated either by surgery or radiation or both.

In a consecutive series of 73 cases of Ewing's sarcoma with microscopic

confirmation that were treated at Memorial Hospital between 1918 and 1942, there were only 3 who survived five or more years after definitive treatment without evidence of recurrence or metastases. Two of these cases received toxin therapy in addition to surgery, roentgen therapy, or both. However, during this period more than half of all our cases were given toxins as a part of their treatment.

In 1940 figures compiled from the Bone Sarcoma Registry indicated only 11 cases of Ewing's sarcoma that had survived more than five years. Six of these 11 cases had been treated with toxins, yet in none was this the sole method of treatment.

Moreover, in the period from 1935 to 1940 there were 125 cases of osteogenic sarcoma of which 82 received no toxins and there were 12 five-year survivals (15 per cent); 43 received toxins and there were 11 five-year survivals (25 per cent).

Admitting the difficulty of drawing conclusions from statistics such as these, and granting that in none of these cases were the toxins used as the sole method of treatment, one may infer that unless some unconscious or deliberate selection was made of the cases in which the toxins were used or withheld, this agent (toxins) played a definite part in the higher survival rate. The toxins may have favorably influenced survival by their effect upon minute pulmonary metastases, preventing them from establishing themselves in the lungs or elsewhere. Perhaps, therefore, the tumor-hemorrhage producing factor in the toxins, as shown by Shear and others, caused necrosis of tumor cell emboli and were thus responsible for some of these survivals.

Our conclusions may be briefly summarized as follows:

1. It is our impression that the more cellular, anaplastic, and clinically malignant the tumor, the more reason for employing the toxins. It seems unlikely that they are beneficial in the low-grade sarcomas. Of all the types, we have found the most favorable results were obtained in primary reticulum cell sarcoma of bone. Their use in cases of Ewing's sarcoma is also recommended.

2. A few extraordinary cases have been observed in which one cannot escape the conviction that the recovery was due solely to the effects of the toxins. A striking example is the case reported by Christian and Palmer in which a very extensive recurrent reticulum cell sarcoma of the tibia with multiple metastases received no other treatment than injections of *Coley's Toxins* in large doses over a considerable period. All the growths regressed, the patient recovered and is well now, twenty-one years later. Additional cases in which the results were striking were reported by Johnson, Greenwood, Mynter, Walton, Winberg, Lilienthal, and others.

3. When used after extirpation of the primary tumor or in conjunction with roentgen therapy the toxins have failed in the majority of cases to

prevent the development of distant, fatal metastases. Nevertheless from the figures cited above it may be inferred that in a worthwhile percentage of cases toxin therapy may inhibit and even prevent the development of minute tumor emboli in the lungs or elsewhere.

4. Toxin therapy with the preparation available from 1921 to 1946 was not considered as indicated without some other form of treatment designed to remove or destroy the primary growth. As a prophylactic against recurrence following surgical removal its use appears to have been justified. If future preparations of Coley's Toxins or other more potent bacterial products become available, their use as the only form of treatment may be indicated.

5. Because in some instances toxin therapy was withheld until the disease had reached an advanced or even hopeless stage, and because it had so often been given for brief periods and in conjunction with other methods of treatment, it is suggested that future trials of the method be instituted at an early stage of the disease and that other methods, i.e., surgery or radiation, be withheld for a short period of time until it is possible to gauge the effectiveness or ineffectiveness of the toxins. Needless to say a microscopic confirmation of the diagnosis should be obtained in every case prior to treatment.

It would appear that the general principle of antibiotic treatment of malignant tumors deserves further extensive study. It is quite possible that as a result of such a study there may be developed a product capable of exerting a more uniform therapeutic effect in a high percentage of cases which the present preparations admittedly have not accomplished.

TECHNIC OF ADMINISTRATION OF COLEY'S TOXINS

While the toxins have been administered by various routes, i.e., intramuscular, intratumoral, and intravenous, our present feeling is that the intravenous route is the most effective. The dosage is of particular importance because of the violent reactions which follow an injection given into a vein. For adults in good general condition it is safe to commence with a dose of $\frac{1}{80}$ minim, while for children $\frac{1}{100}$ minim is considered appropriate (in both instances diluted with normal saline solution up to 8 or 10 minims). At first the injections are given daily and the dose is increased cautiously, i.e., M. $\frac{1}{80}$, $\frac{1}{60}$, $\frac{1}{40}$, etc., as the effects of the preceding one become less pronounced. The aim is to produce a reaction evidenced by a chill and a rise of temperature to 104° or 105° . With such a response the dose should be repeated, and increased only when a less violent effect is obtained. Thus one decides upon each successive dose only after observing the effect of the preceding one. Usually a patient can tolerate daily injections but if an unusually severe reaction is produced a day's interval of rest may be desirable.

Accurate measurements are facilitated by the use of a Luer tuberculin syringe which is graduated to half minims. If there is leakage outside the vein local soreness and redness and some swelling will result.

The toxins should be kept in a refrigerator except when in actual use. The bottle should be shaken well each time, and should be discarded *before the expiration date is reached*.

The intravenous route demands hospitalization of the patient or at least constant trained nursing attention. The temperature and pulse should be recorded every hour up to eight hours after the injection or until they are found to be approaching normal levels.

Herpes of the lips is a not infrequent sequela of a severe reaction to the toxins but it usually disappears promptly without special treatment. Because severe reactions are often attended by a pronounced fall in blood pressure and a weak and rapid pulse which may persist for several hours after the chill, there is some risk in the use of toxins in elderly patients or in those in advanced stages of the disease. If used at all under such circumstances great caution in the selection of the initial and subsequent doses is essential.

59. BIOCHEMICAL TREATMENT OF TUMORS OF BONE

WHILE INVESTIGATING THE EFFECTS OF CERTAIN BACTERIAL PRODUCTS ON tumors in animals Shear and Andervont found that they could separate the hemorrhage-producing factor from toxic and inert fractions of filtrates of broth cultures of *E. coli*. Thus they were able to produce a preparation with a high potency. Later Shear and his co-workers elaborated a potent polysaccharide from a filtrate of cultures of *Bacillus prodigiosus* (*S. marcescens*). Both these agents were found to produce hemorrhage in transplanted sarcomas in mice.

Brues and Shear have described the effect of injections of the said polysaccharide upon four patients suffering from various forms of malignant disease; all were inoperable, had extensive metastases, and were deemed unsuitable for further radiotherapeutic measures. These cases consisted of prostatic cancer, multiple myeloma, lymphosarcoma, and Ewing's sarcoma. All four patients died of their malignant diseases. Two however showed noteworthy relief of symptoms. The patient with multiple myeloma showed no effect of the injections on the tumor. Two at autopsy revealed evidence of intratumoral hemorrhage; it was not possible however to state that the hemorrhage was related to the treatment.

In the course of treating these cases Brues and Shear noted the following clinical manifestations: chill followed by febrile reaction of about 4° F. above previous level; leukocytosis associated with the appearance of 1 to 5 per cent of immature cells of the myeloid series; no evidence of blood destruction despite a 15 to 25 per cent fall in red cell count and hemoglobin; increase of sedimentation rate to extremely high levels; decrease in platelet counts and a tendency to bleed in the 2 cases that received repeated doses; marked hypotension in 3 of the cases, associated with anuria in 1, and cardiac decompensation in the 2 older patients. Evidence of tissue breakdown was seen in the rapid and marked increase in nonprotein nitrogen and uric acid in the blood of 2 patients and their increased excretion in 1 case. Coincident with these chemical evidences of tissue breakdown was symptomatic relief. Proof of cause is lacking that the inferred tissue breakdown

was confined to tumor tissue. In the lymphosarcoma case regression of enlarged lymph nodes remote from areas of recent roentgen therapy was noted and one of the tumors developed a hemorrhage.

This report of Brues and Shear deserves consideration for the following reasons: (1) it points out some of the hazards of therapy by means of bacterial toxins or chemicals derived from bacterial products; (2) it shows that clinical improvement was produced in 2 of the 4 cases and regression in the size of the tumors in 1 instance; (3) it tends to support the experimental work done on animal tumors; and (4) it indicates that further research along these lines would seem to be fully justified in the expectation of discovering a chemical product which has an effective tumor-destroying property.

60. TREATMENT WITH RADIOACTIVE ISOTOPES

IN RECENT YEARS EFFORTS HAVE BEEN MADE TO TREAT CERTAIN FORMS of cancer by means of radioactive isotopes. If an isotope can be found which will be taken up selectively by cancer cells, then the radiation from the isotope will be more intense in the tumor tissue than in adjacent normal structures. If a sufficiently high degree of selective uptake can be obtained, then therapeutic doses of radiation can be administered to the tumor without undue exposure of normal tissue.

Radioactive phosphorus has been tried in the treatment of bone sarcoma. Since this substance is an isotope of normal phosphorus, it is deposited in high concentration in any tissue where normal phosphorus is being stored rapidly. In most osteogenic sarcomas abundant new bone is being formed, and this tissue takes up radioactive phosphorus much more rapidly than normal bone or soft tissues. It has been found possible to administer a dose equivalent to 500 r to some osteogenic sarcomas by means of radioactive phosphorus without exposing the rest of the body to dangerous amounts of radiation. Unfortunately osteogenic sarcomas are so radioresistant that doses of this order are of little value. In endothelioma of bone and other bone tumors in which little new bone is formed the uptake of radioactive phosphorus is small, so that, although these tumors are more radiosensitive than osteogenic sarcoma, it is not possible to administer therapeutically effective doses of radiation to them by means of this isotope.

Certain types of thyroid cancer retain the capacity of normal thyroid tissue to store iodine. In such cases both the primary tumor and the distant metastases take up radioactive iodine with a very high degree of selectivity. Recently Higinbotham and others have obtained striking control of bone metastases from thyroid carcinoma by means of radioactive iodine given by mouth. The method shows great promise, and may become an established therapeutic procedure in suitable cases in the future.

At present (1947) the study of the therapeutic possibilities of radioactive isotopes is in its infancy. Further work may show that they have a wide field of usefulness.

RADIOACTIVE STRONTIUM

Radioactive strontium was first described by Stewart, Lawson, and Cork. It is prepared by bombardment of metallic strontium with 16-million-volt deuterons in the 60-inch cyclotron (at Berkeley, California). Its maximum uptake occurs in bone and tumor tissue and in skin.

In an article entitled *Metabolic studies on neoplasms of bone with the aid of radioactive strontium*, Treadwell, Low-Beer, Friedell, and Lawrence demonstrated that there appeared to be some selective uptake of radioactive strontium in bone tumors. However in a personal communication one of these authors (Friedell) indicated that this differential was not great enough to warrant the extensive radiation which occurs to the remainder of the skeleton.

61. OTHER TYPES OF TREATMENT

TREATMENT BY THERMAL METHODS— CRYOTHERAPY

FOR A BRIEF PERIOD THE APPLICATION OF THE PRINCIPLE OF PROLONGED hypothermia in the treatment of cancer was tried. Temple Fay in Philadelphia was one of those who became interested in this form of therapy and it was used for cases of cancer of all varieties. Two methods of refrigeration were employed, the first involved maintaining a lowered temperature of the body as a whole, while the second concerned the attempt to produce lowered temperatures in the affected part, e.g., in an extremity which was the site of a sarcoma.

While it was found that an analgesia and a retardation of the tumor growth were produced during the period while the limb was being cooled, there were no striking benefits of a lasting nature and the method was soon abandoned. At present it is only of historic interest.

CHEMICAL METHODS: TREATMENT WITH COLLOIDAL LEAD

Twenty years ago the use of intravenous injections of colloidal lead in the treatment of cancer was advocated by Blair Bell. It was used mainly in conjunction with irradiation by the radium element pack or roentgen rays. A trial of the method was made at Memorial Hospital, and several cases of bone sarcoma were given this combination therapy. About one-quarter of the patients showed transitory improvement which appeared to be due to the lead, but side reactions were frequent and dangerous, and the method was discarded after a short-lived popularity. It is mentioned only to be condemned and for its historic interest.

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SECTION TEN

Lesions of the Skeletal System That May Simulate Neoplasms of Bone

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INTRODUCTION TO SECTION TEN

IT HAS SEEMED WORTHWHILE TO CONSIDER THE MANY BONE DISEASES simulating tumors of bone, since they may at times, and with varying degrees of frequency, require differentiation from true tumors. This is borne out by the fact that the majority of lesions discussed have been ob-

TABLE XLVII
NONNEOPLASTIC CONDITIONS OF BONE SOMETIMES CONFUSED WITH
TUMORS OF BONE

NONNEOPLASTIC CONDITIONS	BONE TUMORS
<i>Infections</i>	
Pyogenic	Endothelioma (Ewing's sarcoma)
Typhoid	Myeloma
Tuberculosis	Myeloma (spine)
	Chondrosarcoma
Syphilis	Osteogenic sarcoma
Yaws	Osteogenic sarcoma
	Endothelioma (in children)
Chronic sclerosing osteitis	Sclerosing osteogenic sarcoma
<i>Parasitic diseases</i>	
Hydatid disease	Osteolytic osteogenic sarcoma
	Metastatic carcinoma
<i>Cystic diseases</i>	
Solitary bone cyst (unicameral)	Central chondroma
	Giant cell tumor
Hyperparathyroidism	Metastatic carcinomatosis
<i>Diseases of uncertain etiology</i>	
Fibrous dysplasia.	
Osteitis deformans	
Leontiasis ossea	Metastatic carcinoma metastases (polyostotic)
Osteoid osteoma	Lowgrade osteogenic sarcoma of facial bones
Melorheostosis	Sclerosing osteogenic sarcoma
Hand-Schüller-Christian's disease	Osteogenic sarcoma
Eosinophilic granuloma	Metastatic carcinoma
Spontaneous Absorption of Bone	Myeloma (in late life)
	Endothelioma (Ewing's sarcoma)
<i>Lipid storage diseases</i>	
Gaucher's disease }	Metastatic carcinoma
Niemann-Pick's disease }	
<i>Diseases due to circulatory disturbances in bone</i>	
Aseptic necrosis	Benign chondroblastoma
Calcinosis (tumoral form of Inlcan)	Sclerosing osteogenic sarcoma
<i>Diseases due to injury</i>	
Ossifying hematoma	Osteogenic sarcoma (in early stages)
Fatigue fractures }	Osteogenic sarcoma (in active reparative phase)
Perosteal tears }	

served in the Bone Tumor Clinic of Memorial Hospital where the patients have been sent by their physicians and by other clinics on the assumption that their condition might represent a neoplasm of bone.

Again, since these diseases may simulate neoplasms, the surgeon or radiotherapist whose interest lies in the field of *bone tumors* may have to study and diagnose them and at times he may even have to treat them. Moreover, a considerable number of them have been known to be, on rare occasions, complicated by superimposed malignant bone lesions. This is notably true of Paget's disease of bone, although instances of this sort have been personally observed and reported by others in connection with aseptic necrosis, osteopetrosis, and Gaucher's disease. A summary of the nonneoplastic conditions with those conditions which they may simulate is given in Table XLVII.

The importance of the conditions cited in this section from a *differential diagnostic standpoint* varies considerably. Some are encountered with comparative frequency and others so rarely as to raise the question of the propriety of including them at all. Examples of the former are: myositis ossificans, the osteomyelitides, and the granulomas, e.g., eosinophilic granuloma and Hand-Schüller-Christian's disease; of the latter, especially in North America, one might mention osseous hydatid and yaws; and regardless of the geographical location, such conditions as melorheostosis, osteogenesis imperfecta, spontaneous absorption of bone, and leontiasis ossea. Those which are commonly encountered in a bone tumor clinic are dealt with in considerable detail while some of the rare and less important conditions are referred to but briefly. Many have been mentioned earlier in connection with the neoplasms with which they may at times be confused.

62. CONDITIONS DUE TO BONE INFECTION

PYOGENIC

ACUTE HEMATOGENOUS OSTEOMYELITIS

BECAUSE HEMATOGENOUS OSTEOMYELITIS MAY OCCASIONALLY BE MISTAKEN for primary bone sarcoma it is necessary to point out the fact that these two conditions have certain points of similarity.

Cases of severe or fulminating osteomyelitis have such a sudden onset and such profound constitutional symptoms and signs that the diagnosis of sarcoma is seldom tenable. Instances of milder infection with insidious onset, on the other hand, may present few general symptoms or signs of infection and the predominating manifestations are local. It is in such cases that a mistake in diagnosis is readily made, especially when seen at a time when the earliest recognizable roentgenographic changes appear. Not infrequently the experienced roentgenologist and clinician are both uncertain and a definite diagnosis is only assured by the subsequent course of the disease or by microscopic examination.

Hematogenous osteomyelitis has the following features that are common to bone sarcoma: It is most often observed in childhood and adolescence which is the same period in which bone sarcoma is prevalent; it is characterized by the same triad of symptoms, pain, swelling, and disability; it is often preceded by a history of local injury; it affects the same sites in the same bones where sarcoma most often arises. However it differs from bone sarcoma in having a more rapid onset, being accompanied by fever and leucocytosis, and by the frequent history of an antecedent staphylococcic furuncle or other focus of infection.

Milder forms of osteomyelitis may closely simulate Ewing's sarcoma because the patient's general condition is good, signs of infection may not be evident, temperature and leucocyte count may be only slightly elevated, and the chief complaint is pain in the affected extremity (see Fig. 306.)

Early in the course of an acute osteomyelitis films may reveal no altera-

tion, however within a week to ten days there may be visible bone changes characterized by destruction and by newly formed reactive bone (see Figs. 307-9). The earlier these findings are seen the more they may resemble bone sarcoma.



FIG. 306. Low-grade subacute osteomyelitis of tibial diaphysis in a young female closely resembling endothelioma; culture revealed staphylococcus.

Since osteomyelitis decreases rapidly in frequency after the age of 16 it deserves consideration chiefly in cases of children.

CHRONIC SCLEROSING OSTEITIS

Although sclerosis may be a prominent feature of a healed osteomyelitis which formerly supplicated extensively, the nonsuppurative form which affects a single bone and is not accompanied by drainage is the one which needs to be distinguished from osteogenic sarcoma, osteoid osteoma, and occasionally from syphilitic osteitis.

In 1893, Garré, in a communication dealing with acute osteomyelitis, described the nonpurulent, sclerosing form which he defined as "those infectious forms of osteomyelitis which leave behind solely swelling and thickening of bone without formation of either pus or of fistulas. They begin in a typical way, having an acute onset in the majority of cases, proceed with high fever, swelling of the extremity, pain, and swelling of the bone, even with considerable soft part infiltration which leads to the expectation of speedy abscess formation. Yet the infiltration regresses slowly after the fever has subsided and as the patient gradually recovers nothing remains but a variable degree of swelling of the bone."

Symptoms and Signs

Persistent pain of a severe degree, deeply located, more troublesome at night, made worse by activity or injury, with some changes in intensity, is the earliest and, indeed, often the only complaint. Swelling may

be present. It is stony hard, not changing in size over long periods of time,

and tender on deep pressure (a finding that depends somewhat on the location of the lesion, being more readily palpated in the shaft of the femur or of the tibia). Ordinarily disability is not prominent and adjacent joints have un-



FIG. 307

FIG 307. Osteomyelitis with pathologic fracture closely simulating a malignant tumor. At the clinical conference where this patient was presented the consensus was strongly in favor of a diagnosis of malignant neoplasm. Patient well sixteen years later.



FIG 308

FIG. 308 Pyogenic osteomyelitis. The organism in this instance was hemolytic staphylococcus aureus.

impaired function. Soft parts overlying the area are not involved, maintain a normal appearance, and feel normal on palpation. There is no obvious impairment of general health.

Clinical Features

There may be no recollection of any acute illness which represented the initial onset of the condition. Persistent questioning of the patient or of his relatives, however, may elicit a history of a mild illness or of local antecedent injury.

The chronicity of the pain and swelling suggests the diagnosis, but it can

generally be corroborated by roentgenographic examination. Films reveal a smooth outline of the expanded shaft without destructive or productive changes, and the cortical outline is unbroken. The sclerosis is uniform, the

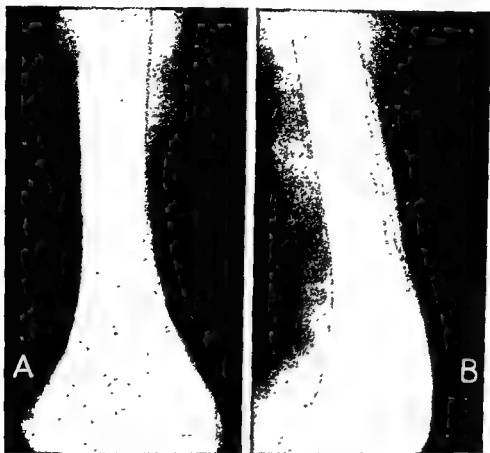


FIG. 309. Acute osteomyelitis resembling endothelioma. A, Note the cortical and sub-cortical involvement. At this stage the process is extremely difficult to distinguish from endothelioma. Penicillin was given and the infection did not go on to frank suppuration. B, Lateral view of the same case. Taken a few weeks later, it shows a more extensive process, still resembling endothelioma.

periosteum is not appreciably thickened, although the medullary portion of the bone may be markedly encroached on by cortical thickening (see Figs. 310 and 311).

At times a small, circumscribed area of radiolucency is seen in films made to show bone rather than soft part detail. These may represent foci where bone has been destroyed. However, cultures from such areas do not often yield positive findings.

Differential Diagnosis

Sclerosing osteitis may resemble osteogenic sarcoma. Amputation had been recommended for one patient that was personally observed and treated, but the absence of either destruction or irregular production of bone in this condition was strong evidence in favor of osteitis rather than sarcoma.

Osteoid osteoma, on the other hand, may present an extremely difficult diagnostic problem, for the sclerosis is quite similar, and a translucent area in the sclerosing portion of the bone which represents the so-called nidus

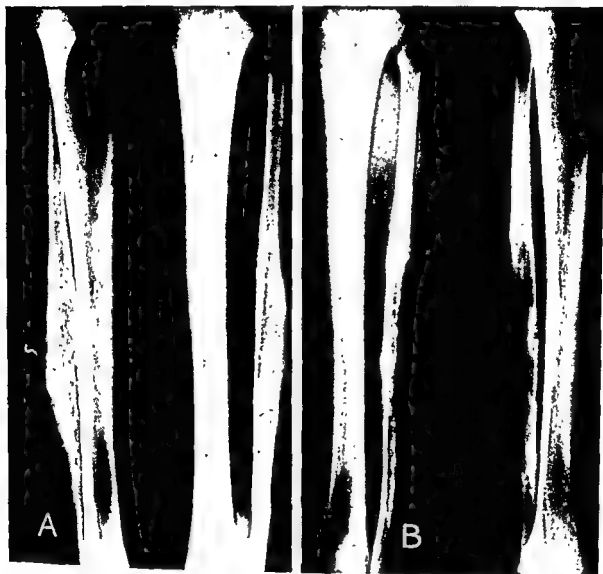


FIG 310. A, Chronic sclerosing osteitis of fibula. Before operation. B, Same case after excision of diseased segment.

may be mistaken for areas of decreased density occasionally seen in sclerosing osteitis. It is highly probable that many cases regarded in the past as being sclerosing osteitis were in reality instances of osteoid osteoma. In fact, there may well be a close connection between the two conditions. Certainly one should bear both of these lesions in mind whenever a localized sclerosing condition of bone is encountered. Brailsford has voiced the opinion that osteoid osteoma may be a phase of chronic subperiosteal abscess. Both conditions yield to similar surgical measures which promote healing by opening of the "nidus" or central cavity either by excision, saucerization, or even simple drilling.

Syphilis, which can imitate almost every type of bone pathology, simulates sclerosing sarcoma at times. However, in syphilis both destructive and productive changes in bone are usually noted; periosteal reaction is more



FIG. 311. A, Chronic sclerosing osteitis of clavicle. B, Appearance of gross specimen. Total excision of the clavicle gave a satisfactory result. (Borden General Hospital.)

pronounced and more extensive up and down the shaft, e.g., the saber shin of syphilis. Serology is important and should be obtained in all cases of unusual bone pathology. Yaws may likewise have to be considered in tropical countries where it is endemic.

Paget's disease (osteitis deformans) is mentioned by some authorities as resembling sclerosing osteitis, but actually the two conditions are not similar and should seldom be confused. Paget's disease is rarely monostotic; it has a pattern of destructive and productive bone closely intermingled. The result is a blurred or fuzzy appearance never seen in sclerosing osteitis. In addition, Paget's disease has a characteristic marked elevation of the serum alkaline phosphatase level which is not true of sclerosing osteitis where the serum phosphatase is normal or very slightly above normal.

While the terminal stage of a pyogenic osteomyelitis following the sup-

purative phase is often associated with intense bone sclerosis, the picture seldom resembles a bone neoplasm. The condition known as sclerosing osteitis, on the other hand, may present features which cause it to be mistaken for a sclerosing osteogenic sarcoma.

Treatment

Sclerosing osteitis, which is discovered accidentally or incidental to some unrelated condition and which is causing no symptoms, requires no treatment. Those cases complaining of persistent pain need surgical intervention. This may consist merely of drilling the involved bone with multiple fine drill holes, such as can be made with Kirschner wires, or it may involve unroofing the area by removal of part of the cortex followed by a saucerization. Extremely extensive procedures are not considered necessary or advisable. The far simpler method of multiple drill holes usually deserves a trial before resorting to the guttering type of operation.

Cultures should always be made, both aerobic and anaerobic, and if positive should be tested for penicillin sensitivity. Upon the results of such tests the question of penicillin therapy can be decided. Sulfonamide treatment is also to be considered. Both these agents, however, would seem to be more important in the acute stage of infection where their wider use may in time result in making chronic sclerosing osteitis a rare clinical entity. Since we are as yet ignorant of the causative organism responsible for sclerosing osteitis it is highly questionable if chemotherapy will be of any value in the absence of positive cultures from the depths of the bone. Further investigation along these lines is needed.

CENTRAL BONE ABSCESS (BRODIE'S ABSCESS)

Central bone abscess, first described by David, elaborated by Vidal-Naquet, and again by Benjamin Brodie, has generally been referred to as Brodie's abscess. It is a chronic process usually limited to a single bone, most frequently the tibia, although the femur, humerus, and radius may be affected. It is usually manifest during adolescence or early adult life. It is located at the site at which ordinary hematogenous osteomyelitis is found, namely, the metaphysis. It develops in the medullary portion of the bone but exhibits no tendency to invade the epiphysis whose cartilage plate appears to offer an insurmountable barrier to extension. Pus is contained in its medullary canal but there is no subperiosteal abscess. In the long-standing case the bone itself may be slightly expanded and the abscess cavity has well defined margins (see Figs. 312 and 313). The organism generally recovered is staphylococcus aureus although in cases of long duration cultures may be sterile. Subperiosteal bone formation and sequestration, as seen in conventional hematogenous osteomyelitis, are not found in Brodie's abscess.

Clinical Features

The most constant symptom is pain which may become so severe as to prevent sleep. Slight increase in the size of the bone as determined by palpation is a suggestive but inconstant finding. The adjacent joint is unaffected while the patient's general condition is seldom impaired. Roentgenographic features are usually fairly typical. Conditions with which it may



FIG. 312. Bone abscess. Symptoms are dull pain, especially on activity, but no evidence of inflammation in soft tissues. The affected tibia is one inch longer than the normal one. The appearance is similar to that of an osteoid osteoma.



FIG. 313. Bone abscess, healed obsolete stage. Note resemblance to aseptic necrosis such as is seen in caisson workers.

be confused are syphilitic osteitis and yaws. Eosinophilic granuloma provokes a much less well-marked peripheral zone of reactive bone. Rarely

it may resemble a medullary chondromyxosarcoma. Treatment is surgical and simple drainage of the abscess is generally sufficient to result in complete healing. It is usually possible to evacuate the cavity and close the



FIG. 314. Syphilitic dactylitis.

wound primarily, and with the advent of chemotherapeutic agents this method should be still more successful.

SYPHILITIC OSTEITIS

In its tertiary stage syphilis attacks bone with great frequency although its osseous manifestations may not be recognized. Campbell stated that skeletal involvement was present "in a very large percentage of those affected with syphilis."

The most bizarre types of bone involvement are produced by this disease (see Figs. 314-317) and it is for this reason that we must always have it in mind when dealing with a suspected bone lesion.

CLINICAL TYPES

Luetic destruction may affect one small area in a single bone, may be widespread throughout an entire bone, or scattered in several bones. In congenital syphilis the nasal bones and radius are common sites as are the phalanges.

During a twenty-five year period we have observed a few cases where syphilis was easily confused with bone tumor. It is desirable to perform



FIG. 315. Syphilitic osteomyelitis involving the right tibia and the left fibula in the same individual.

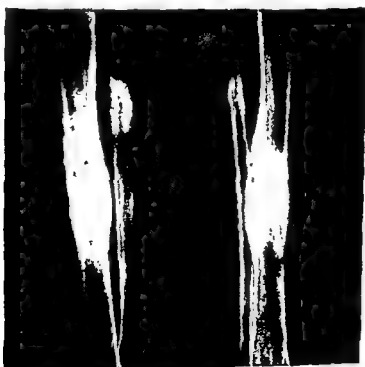


FIG. 316. Syphilitic osteitis of tibia and fibula.

positive reaction in spinal fluid is conclusive of syphilis. Yaws does not produce congenital disease but children may contract the infection early. It enters the body through a trivial break in the skin such as an abrasion or

cut and a primary sore results. Secondary manifestations occur in a few months when skin eruptions which itch are readily diagnosed signs of generalization. These make the patient quite uncomfortable.

The next stage, corresponding to tertiary lues, may not appear for a number of years. It is characterized by callous ulcers more often of the lower extremities. The long bones may be painful and the soles of the feet exhibit painful depressed areas. Joint deformities may exist. Overlying soft parts may be inflamed and skin reddened and edematous. Gangosa and goundou are rare but striking forms of this disease.

The tertiary stage presents bony lesions which are our principal interest in this disease since it is possible that following World War II we may encounter these cases in other than tropical areas.

This disease may be a cause of joint pain, backache, skull, or chest pain. It is divided into active and inactive

phases and the roentgenographic appearance of bony lesions varies according to the phase. The inactive phase differs from the active chiefly in the absence of local pain, edema, febrile reaction, positive serology, and rapid response to spirocheticidal therapy. Inactive cases have vague pains, a generally lowered vitality, frequently a positive Kahn reaction, and a history of previous infection.

Helfet, in describing acute manifestations of bone and joint yaws, considers it the most ubiquitous disease of bones and joints in the tropics. Its manifestations being so similar to syphilis adds to the difficulties in diagnosis. Though yaws seldom affects viscera, as does syphilis, both conditions are prone to attack bones and joints.

Helfet has studied especially the acute phase of bone and joint involvement. Here he believes that the pain in yaws is more acute and severe than in that deep-seated aching characteristic of bone sclerosis from syph-



FIG. 318. Charcot shoulder. The roentgenographic appearance is not incompatible with a destructive malignant tumor.

ilis. In fact, where a long bone is concerned the intense pain, swelling, and febrile reaction resemble a septic osteomyelitis.

Antecedent trauma is so often found in the history, and so often is severe,



FIG. 319. Charcot ankle.

that its role as a localizing factor in an otherwise latent, though generalized, disease cannot lightly be discounted.

Since acute yaws in bone may have its onset with fever and generalized "rheumatic" pains, and since chronic malaria with the same endemicity has similar features, it happens that yaws is often diagnosed as such and anti-malarial therapy instituted.

Sites of election are: the tibia, the clavicle (inner end), and the humerus (lower third). Invariably the bone lesion fails to ulcerate through the skin. Serology is always positive (Wassermann, Kahn, etc.).

Tendon sheaths, bursae, and joints are affected; at times both dorsal tendons of wrists and of feet may be simultaneously involved. The joint and synovial-sheath manifestations of the disease are chronic and relatively without pain. Synovia are thickened and villi hypertrophied as seen grossly at arthotomy and as verified microscopically.

ROENTGENOGRAPHIC APPEARANCE

The alterations closely resemble those seen in syphilis and include widening of the shaft and dense sclerotic bone with some areas of punched out radiolucency. In the acute form of yaws, however, there is evidence of subperiosteal necrosis, elevation of the periosteum often with expansion, and periosteal new bone formation laid down in the lamellated fashion characteristic of Ewing's sarcoma (onion-layer appearance). The newly-deposited periosteal bone may occasionally resemble osteogenic sarcoma.

Inactive yaws is characterized by a dense, eburnated bone which presents roentgenographic features resembling an old healed osteomyelitis.

Untreated cases of long standing may reveal characteristics of a dense sclerosing osteogenic sarcoma or a sclerosing osteitis of Garré type (see Fig. 320). More often the lesions require differentiation from acute osteomyelitis, tuberculosis, syphilis, and bone changes due to avitaminosis.



FIG. 320. Osseous lesions in yaws. Subject was a New Guinea native without symptoms. Note resemblance to luetic bone involvement and the fact that both tibia and fibula are bilaterally affected.

In children of tropical countries the difficulty of distinguishing yaws from endothelioma or osteogenic sarcoma may be great; serology in such situations is of great importance.

TREATMENT

Arsenicals clear up the acute symptoms rapidly but the objective findings, especially swellings, are slow to subside. Within a week or two after arsenical therapy the pain and malaise are gone and a sense of well-being is restored. Soon thereafter tenderness fades and only swelling persists.

TUBERCULOSIS OF BONE

While bone tuberculosis is often mentioned as one of the conditions which must be thought of in the differential diagnosis of tumors of bone it has not been frequently encountered as a difficult problem at Memorial Hospital. This may be due in part to the fact that in New York City the incidence of bone and joint tuberculosis has been steadily decreasing during the past quarter of a century and it is now considered a relatively infrequent cause for admission to orthopedic hospitals. Fifty years ago, on the other hand, when bone tuberculosis was common and before the advent of roentgenographic examination, many a case of bone sarcoma was treated by plaster encasement on the supposition that it was tuberculosis and recognition of the lesion as a neoplasm was indefinitely postponed.

Undoubtedly in other countries where it is still of relatively greater importance it may have to be considered more seriously in cases suspected of having malignant disease of bone. Girdlestone has accurately stated that "the symptoms and clinical signs of a sarcoma or a secondary carcinoma may closely simulate those of tuberculosis [of bone]. Fortunately they can almost always be distinguished from tuberculosis by radiography."

The age at which bone tuberculosis is most often recognized is that at which primary bone sarcoma is most common. Certain features serve to

differentiate the two conditions. The local symptoms may be indistinguishable in that pain may be referred to the neighboring joint, but muscle spasm is usually present in tuberculosis and often entirely lacking in sarcoma. Atrophy of muscle groups is common to both conditions. Sarcoma of the spine is rare whereas this is the most frequently affected site in skeletal tuberculosis. Conversely the upper humerus is seldom the site of bone tuberculosis but is often involved in sarcoma. Malignant synovioma is more difficult to differentiate from bone tuberculosis in those cases where it is associated with destruction of the joint surfaces and adjacent bone.

Systemic features are important in establishing the diagnosis of tuberculosis for there is an afternoon rise in temperature and a history of weight loss which in the early stages of bone sarcoma are generally lacking. Roentgenographic examination is of paramount importance for if it reveals destruction of the bones on both sides of the articulation it is strongly corroborative of tuberculosis since it is almost never seen in sarcoma. Aspiration biopsy is of great value and should yield material both for culture and for histologic study.

Occasionally tuberculosis affects an area in the shaft of the bone (see Figs. 321 and 322) at some distance from the joint and in such rare instances the similarity to an osteolytic sarcoma, Ewing's sarcoma, or even a reticulum cell sarcoma may make differential diagnosis impossible until microscopic examination of tissue has been made.

Dactylitis in children (*spina ventosa*) may be due to tuberculosis but malignant bone tumors of the phalanges are almost never seen. We observed a lesion in the terminal phalanx of the thumb in a young adult which was puzzling until the pathologist suggested it was tubercular after receiving material from aspiration biopsy. In this case subsequent operation confirmed the opinion.



FIG. 321. Tuberculosis of tibial shaft. Diagnosis confirmed by microscopic examination.

SARCOIDOSIS (BOECK'S SARCOID) OF BONE

Sarcoidosis is an obscure and comparatively uncommon disease whose etiology is still unsettled, but as it often gives rise to bone lesions it is referred to here. While the etiologic factor is considered by many to be a non-virulent tubercle bacillus others consider it as an infectious granuloma due to a virus infection.

This disease affects young adults, and Negroes are thought to be particularly susceptible although it is by no means confined to that race. It has an insidious onset and pursues a rather indolent course involving skin, lymph nodes, lungs, and bones. In 35 cases of sarcoidosis Besnier found that there were bone lesions in 9.

Jungling first described the bony manifestations separately and gave us the term "osteitis tuberculosa multiplex cystica."

The medullary portion of the bone is the usual site and cystlike areas of radiolucency are typical. Sometimes these are surrounded by a zone of increased density. The areas are usually small, often multiple, and occur principally in the small bones of the fingers and toes (see Fig. 323). Boone and Coleman call attention to the "painless, rubbery, spindle-shaped swellings of the finger bones." The histologic appearance is

FIG. 322. Tubercular osteitis of radius confirmed by guinea pig inoculation.

characteristic and biopsy should establish a correct diagnosis. Treatment is as yet empirical for no method has been successful. With our present knowledge, no attack upon the bone lesions is justified.

ACTINOMYCOSIS OF BONE

There are occasional cases in which the diagnosis of a destructive bone lesion may be difficult owing to the similarity that may exist between bone neoplasms and actinomycosis of bones and joints.

Bone actinomycosis may be considered under three categories: primary infection of bone, secondary involvement by encroachment of the disease from adjacent soft tissue, and metastatic foci.

The specific infection of bone caused by actinomycosis usually begins as a periostitis from direct extension from contiguous soft tissues and arises only very rarely in bone itself. It usually remains a superficial process in-

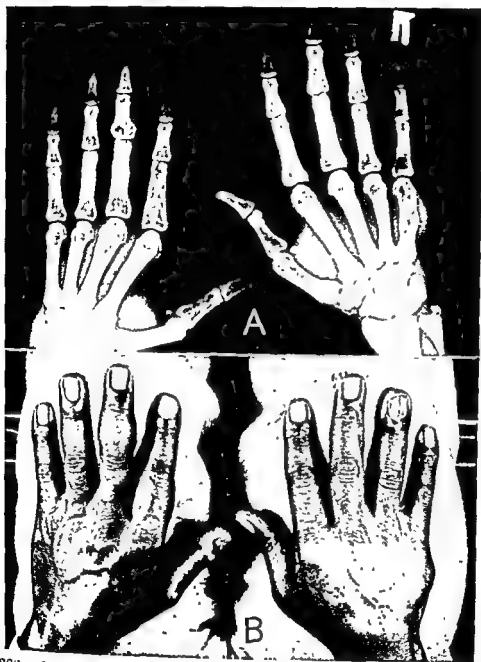


FIG. 323 Sarcoidosis of bone. Note particularly the involvement of the proximal phalanx of the left index finger, the middle phalanx of the left middle finger, the phalanges of the left thumb, and the fifth metacarpal of the right hand. (Courtesy of Dr. John A. Boone, Charleston, S. C.)

volving the periosteum and cortex over large areas with many small abscesses and connecting sinuses. Pus formation is minimal.

Bones most frequently affected are the vertebrae, sternum, ribs, and jaw. Metastatic abscesses from pulmonary foci to the femur have been reported. In general, the affected bones are those in proximity to the tissues which

serve as the portal of entry, i.e., the peribuccal tissues, lungs, and the cecum.

When the vertebrae, ribs, or sternum are involved the diagnosis may not be readily apparent and bone destruction may simulate a metastatic, or even a primary, bone neoplasm.

The lower jaw is the most frequent, if not the only, site of primary infection of bone. Here it occupies a central position which causes rarefaction and sometimes dilatation of the bone. Eventually a bone abscess results, its contents containing actinomycotic pus. Egg-shell crackling, due to extreme thinning of the overlying cortex, has been described by Cope and Meyer-Bostel. Although roentgenographic examination will disclose the area of radiolucency the diagnosis usually will be made only after surgical exploration. Among the rare cases is the one recorded by Williams whose patient developed the disease in one of the phalanges of a finger following a bite.

Where actinomycosis affects bone by contiguity it produces a reactive or irritative subperiosteal proliferation. This may be seen in the mandible where roentgenograms will reveal a superficial zone of new bone formation usually without actual erosion.

In the case of thoracic actinomycosis, erosion of vertebral bodies may accompany new bone formation. The bone changes show less sclerosis than is usually seen in syphilis while there is not observed the predilection for certain parts which is characteristic of tuberculosis. The true nature of the condition usually remains unrecognized until pus is obtained.

Metastatic areas are those in which localized foci are found in the medullary portion of long bones or in cancellous areas in short or flat bones. These may be multiple or monostotic.

TREATMENT

Actinomycosis is still a difficult condition to treat even since the advent of potent chemotherapeutic agents.

Gage, Lyons, and DeCamp have emphasized the anemia and reduction in total circulating mass of hemoglobin in patients with refractory actinomycosis. They estimate the need of an average of five liters of blood for cases of severe abdominal or thoracic actinomycosis, and they attempt to restore the total circulating red blood-cell mass to the standard value for the patient's usual weight in health. Increased protein in the diet is also considered desirable. Penicillin in preference to the sulfonamides is the antibiotic of choice for this disease. Surgery consists of removal of accessible granulomatous areas and drainage of abscesses as promptly as possible after correction of the anemia and hypoproteinemia.

BLASTOMYCOTIC LESIONS OF BONE

Among the relatively rare infectious granulomatous lesions of bone must be placed blastomycosis. This disease has been studied thoroughly by Mar-

tin and Smith (1939) who found a total of 80 proved, 163 presumptive, and 104 inadequately described cases. The bones and joints were infected in half of the proved and presumptive cases.

The clinical picture of blastomycosis of bone may be variable or obscure. The lesion may take the form of a periostitis, an osteomyelitis, or even a suppurative arthritis. Bone destruction may be associated with abscess formation. Pathologic fracture may result. The osteomyelitic form is most often found in the epiphyseal area. There may be little tendency to reactive new bone formation. When a bone focus ruptures into surrounding soft tissues or into the contiguous joint cavity destructive arthritic changes may occur.

Bone lesions are most often seen in the spine, ribs, and skull, although cases have been reported involving the tibia, fibula, ulna, clavicle, humerus, ilium, sacrum, and the bones of the feet, hands, ankles, and wrists. In the series studied by Martin and Smith, the kneejoint was affected in 7 cases and the elbow in 6.

The localization of many foci in the epiphyses points to infarction and the wide distribution of the organism in the skeletal system indicates dissemination by way of the blood stream. Contrary to the favorable outlook in blastomycotic dermatitis (infections of the skin) systemic infection is highly fatal. Martin and Smith cite a mortality rate of 92 per cent in the group of patients followed for more than two years from the onset.

When a patient is seen with bone lesions unaccompanied by other evident signs of disease, and before the development of a discharging sinus, a difficult problem may be posed in differential diagnosis, i.e., between primary bone sarcoma and blastomycotic infection. Vertebral lesions may be especially difficult to differentiate from tuberculosis.

SPOROTRICHOSIS

Sporotrichosis is a chronic infection resembling blastomycosis caused by the fungus *Sporotrichum* (see Figs. 324 and 325). Clinically, it is characterized by an initial lesion, usually on the hand and almost always confined to the extremities, which is a small persistent draining nodule similar to the lesion of primary tularemia. After several weeks or months, subcutaneous nodules appear along the course of lymphatics draining the lesion. These secondary nodules enlarge and become fixed to the skin which discolors and ulcerates with the formation of indolent discharging ulcers. Wide dissemination in these forms seldom occurs. At other times, when the primary skin lesion is more fulminant, generalized hematogenous dissemination takes place. Here the subcutaneous nodules appear over the entire body rather than limiting themselves to an extremity. Visceral sporotrichosis may involve bone, lung, muscle, or brain. The course is chronic but rarely fatal. The disease appears to spread after an incision or attempted excision of the lesions.

TREATMENT

Potassium iodide 2-6 gm. daily diluted in water or milk is almost a specific treatment. It should be continued at least one month after apparent

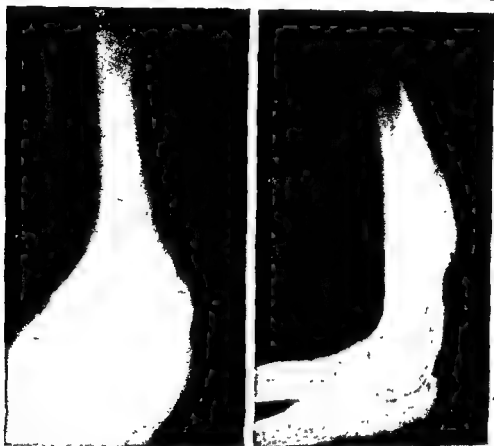


FIG. 324. Sporotrichosis of bone showing productive changes which might be confused with a low-grade osteochondrosarcoma.



FIG 325 *Sporotrichum Schencki*. Microscopic appearance of organism.

recovery. Local lesions may be treated with iodine ointment or tincture of iodine. Penicillin or streptomycin might be of benefit.

CASE REPORT

H.S., a 41-year-old male, was first seen at Memorial Hospital on June 10, 1941, with the history that four years previously he had noted limitation of motion of the right elbow-joint. Roentgenograms were taken at that time, following which he was told he had arthritis and was given diathermy without relief. Shortly thereafter, he began to have nagging pains, which were slightly worse at night and were localized to the right olecranon. The limitation of motion progressed to almost complete ankylosis. Two years prior to his admission, roentgenograms showed early bone overgrowth. About one year later a visible swelling appeared and was progressive. The only significant finding in the past history was that psoriasis had been present for the preceding seven years.

Physical examination revealed psoriatic lesions on the right palm and medial aspect of the left foot. Ankylosis of the right elbow was present. There was a visible, hard, fixed, nontender mass measuring 9 cm. in length extending along the posterior aspect of the humerus (see Fig. 330).

On June 16, 1941, an operation, consisting of removal of the soft tissue for biopsy and curettage of the mass in the bone (also for biopsy purposes) was done. The report was chronic inflammation with degeneration of muscle and fragments of dead bone. A culture taken showed *Sporotrichum Schenckii*. Post-operatively, the patient was started on potassium iodide. While there was regression in the size of the tumor, limitation of flexion and extension persisted with some limitation of pronation and supination. When last examined six years later the condition was found to be practically unchanged.

TORULOSIS OF BONE—CRYPTOCOCCUS NEOFORMANS INFECTION

While infection in the human by the organism *Cryptococcus neoformans* or *Torula histolytica* has been described on many occasions since Zenker's first report in 1861, the first description (and thus far the only one) involving bone is that of Jesse (1947).

His patient, a 24-year-old Caucasian male, complained of pain in the right hip of short duration. Films revealed a cystlike area in the right inferior pubic ramus which was shown by subsequent roentgenograms made two weeks later to have enlarged considerably. Six weeks after its discovery this area was explored and a biopsy taken which was reported as showing histologic features consistent with torulosis of bone. Moreover the culture yielded a growth of *cryptococcus neoformans* which was found to be pathogenic for mice. Treatment consisted of penicillin in a total dose of 1,320,000 units. This resulted in an apparent cure with a follow-up period of more than a year.

Torulosis must be added to the list of mycotic infections which may produce bone lesions which resemble neoplasms. The roentgenograms of

Jesse's patient could readily be construed as representing a malignant tumor, either primary or metastatic.

MADUROMYCOSIS (MYCETOMA, MADURA FOOT)

Maduromycosis is a disease characterized by chronic ulcerative lesions which are destructive and deforming. It is generally found on the foot, and occasionally on the hands or on other portions of the extremities. It is rarely found on the trunk. The causative agent, a fungus, *Madurella*, is identified by small, yellow, brown, or black granules in the pus which discharges from sinuses. It is not pathogenic for animals. The fungus probably grows upon grain and is commonly contracted by agricultural workers who work barefoot.

The disease begins with indolent nodules found in the skin and subcutaneous tissues. The affected part becomes markedly swollen, irregular in outline, and deformed. Sinus tracts develop as in actinomycosis. As increasing numbers of nodules break down, extensive ulcerating fungoid areas are found riddled with sinuses. Between the sinuses are firm areas of fibrous tissue with numerous small, yellow nodules which contain caseous material or yellowish pus. The sinuses are lined with granulation tissue in which there is slight lymphocytic infiltration and blood vessel thickening.

Bone changes are not mentioned by most writers but they were prominent in the films of two cases which were kindly furnished by Dr. C. H. Haynsworth of the University of Georgia School of Medicine (see Fig. 326).

TREATMENT

Since the continuation of the process results in such enlargement and deformity of the part, amputation may be advisable. Other than this, little can be done for relief although Hauser mentions potassium iodide by mouth as having been found to be useful.

COCCIDIOIDAL GRANULOMA OF BONE

Systemic invasion due to coccidiomycotic infection is occasionally responsible for lesions in bones and joints (see Fig. 327). The disease is caused by a fungus which is endemic in the San Joaquin Valley of California and also in certain arid sections of Arizona, New Mexico, Texas, and Mexico. It is called "valley fever," California disease, or coccidioidal granuloma. Cases have been reported from the Chaco region of Argentina and from Italy.

The disease when localized resembles influenza since it affects the lungs to which it gains entrance by inhalation of the spores. Climatic conditions are considered important and Emmons has shown that it is essentially a



FIG. 326 Maduromycosis (Madura foot). Note soft-part swelling best seen in the lateral view, and marked involvement of the tarsals, metatarsals, and phalanges. (Courtesy of Dr. C. H. Haynsworth, University Hosp., Augusta, Ga.)



FIG. 327. Coccidiomycosis of patella. Note the microscopic appearance which is diagnostic, the films show only a destructive process, not distinguishable from other bone-destroying diseases.

rodent disease. When the patient's resistance is overcome the generalized form of the disease gives rise to the coccidioidal granuloma which is a serious matter with upwards of half the cases fatal. One can draw an analogy to the disseminated or miliary form of tuberculosis.

CLINICAL FEATURES

Symptoms of the primary form are chiefly pulmonary and may resemble bronchitis or other mild respiratory disease. In addition there may be chills, fever, malaise, anorexia, and aching in the joints and back. The sedimentation rate is increased and eosinophilia later develops. The coccidioidin test, an allergic manifestation similar to the tuberculin test, is a reliable indication of previous infection.

The granulomatous form may give rise to lesions in other parts of the body, notably the meninges, causing fatal meningitis. Bone and joint involvement was noted eight times in 29 cases recorded by Naffziger, who further stated that 2 cases of simple lesions of an extremity were treated successfully by amputation. Caldwell also reported a cure in a lesion of the toe as a result of amputation of the digit.

Unfortunately there is no specific treatment. Naffziger calls attention to the fact that the resistance of dark-skinned races is low and the proportion of Negroes, Mexicans, and South Europeans who develop the granulomatous form of the disease is high.

The writer encountered a number of primary cases and several of the granulomatous type while serving in the southwest during the Second World War. Figure 327 illustrates one of the latter in which the patella was the site of a focus of this disease.

63. GRANULOMATOUS DISEASES OF BONE OF UNCERTAIN ETIOLOGY

WITHIN THE PAST SIX YEARS A PECULIAR SOLITARY LESION OF BONE HAS been independently described by Jaffe and Lichtenstein and by Obani and Ehrlich. The former investigators termed the condition *eosinophilic granuloma*, and the latter, *solitary granuloma*. By 1943 it had become evident to Jaffe and Lichtenstein that the condition which at first had seemed to be monostotic occurred in multiple areas and that despite the fact that the patient made complaint of only one area it was important to search for other lesions by skeletal roentgenograms.

Following the reports by Farber, Green and Farber, Hatcher, and T. B. Mallory, it became apparent that there was a close relationship between eosinophilic granuloma, Letterer-Siwe's disease, and Hand-Schüller-Christian's syndrome. It now seems reasonable to assume that these conditions represent clinical gradations of some basic disorder. When manifested in infancy or early childhood, often in a fatal form with involvement of both skeletal and soft parts, the terms *nonlipid histiocytosis*, *reticulosis*, or *Letterer-Siwe's disease* is appropriate. When the disorder affects children or adults and assumes a chronic form in which the histiocytic areas undergo collagen or lipid alterations the designation *lipogranulomatosis* or *Hand-Schüller-Christian's disease* is proper. The prognosis is less grave although still uncertain on account of damage to lungs, pituitary, and heart muscle. Finally, the comparatively benign form, localized apparently in the bones and often in a single bone, occurring in children or young adults, is designated as *eosinophilic granuloma*. Radiation therapy, simple curettage, or even spontaneous resolution, serve to bring about healing of the involved areas.

LETTERER-SIWE'S DISEASE

Letterer-Siwe's disease (aleukemic reticulosis—Letterer) or diffuse reticuloendotheliosis (Siwe) or nonlipid histiocytosis (Foot and Olcott) is a

rapidly fatal disease of infancy. It seldom occurs after the age of two years. The clinical features are fever, *generalized skin rash*, *purpura*, and a rapidly developing and severe anemia.

Histologically it is characterized by a marked proliferation of the cells of the reticuloendothelial system, especially in spleen, lymph nodes, and skin.

The process suggests an inflammatory origin, such as an infection, and in some cases exhibits areas of bone destruction apparently identical with those seen in Hand-Schüller-Christian's disease. Wallgren has studied reported cases of these two diseases and has shown that there is a transition from one to the other by insensible gradations. As Mallory has expressed it: "In early infancy a malignant course is invariable, and the patient dies before complete development of the lesion, and before time has elapsed sufficient for secondary lipoid degeneration. In later infancy greater chronicity is the rule and some of the features of Hand-Schüller-Christian's disease begin to make their appearance. From the age of two onward the disease is ordinarily chronic, lipoidal stages develop with considerable frequency, and by the age of three or four the typical picture of Hand-Schüller-Christian's disease is the rule."

HAND-SCHÜLLER-CHRISTIAN'S DISEASE

This disease was first described by Hand in 1893, by Schüller in 1915, and by Christian in 1920.

While solitary osseous xanthoma is encountered with exceptional rarity, *Hand-Schüller-Christian's disease* is undoubtedly less rare than the volume of reported cases prior to 1935 would indicate; during the succeeding decade a considerable number of additional cases have been collected.

The syndrome's classical triad of symptoms consists of defects in membranous bones, exophthalmus, and diabetes insipidus. Cases are seen in which both of the latter two symptoms are lacking for it is obvious that not all skull lesions will produce them and not all of the cases have prominent skull defects. However the skull areas are often prominent, hence the term *geographical skull* (see Fig. 328).

CLINICAL FEATURES

Although usually found in infants and children this disease also occurs in adults; a case in a male aged 51 was cited by Thannhauser and Magendanz. Males are more often affected than females.

The disease has an insidious onset progressing by insensible gradations. Its presenting features, which are responsible for attracting parents' attention, are deformity of the skull, excessive thirst, exophthalmus, gingivitis,

loosening and falling out of teeth, and areas of xanthomatous skin involvement. Anemia is a frequent finding and growth may be retarded without loss of weight. Febrile bouts are sometimes observed and may be mistaken



FIG. 328. Hand-Schüller-Christian's disease. Note maphike appearance of skull in A, and swelling of frontal region in B. The disappearance of the mass is seen in C following roentgen therapy.

for rheumatic involvement since muscle and joint pain may occur coincidentally. Although skin lesions may be absent, when found they take the form of xanthoma disseminata.

BONE LESIONS OF HAND-SCHÜLLER-CHRISTIAN'S SYNDROME

The skull is a frequent site for osseous lesions in this disease but we have observed cases with involvement of many vertebral bodies, and the pelvis and long bones; others report lesions in maxillae, scapula, and ribs. When the skull is affected actual bulging and tumefaction may be obvious. In some cases these areas cannot be seen but are rapidly detected on palpation by means of which the defects are then easily mapped out. Any portion

of the calvarium may be affected and both inner and outer tables are usually destroyed. The sella turcica may be encroached upon and the pituitary dysfunction then gives rise to diabetes insipidus and endocrine disturbances.

ROENTGENOGRAPHIC APPEARANCE

The appearance of the areas of bone destruction is characteristic. In small areas there may be thinning of the cortex with expansion; in more advanced areas the edges show sharply defined borders which simulate bone cysts. The irregularity of the areas, on the other hand, especially in the calvarium, are almost pathognomonic. When the maxilla or mandible is the site of localized destruction teeth may become loosened and fall out. Vertebral bodies soften and compression fractures may result (see Fig 329).

DIFFERENTIAL DIAGNOSIS

Few lesions of bone in this disease offer serious differential diagnostic problems. When the three symptoms composing the classical triad are present the diagnosis is readily made. Metastatic skull defects, plasma cell myeloma, and osteomalacia may present a somewhat similar appearance but the age incidence of these conditions does not coincide with Hand-Schüller-Christian's disease. Roentgenograms of Niemann-Pick's and Gaucher's diseases afford a means of distinguishing the bone lesions of these conditions.

Aspiration biopsy is generally diagnostic as typical foam cells leave little room for doubt; surgical biopsy shows the foam cells diffusely scattered or grouped in clumps or nests in a mesh of granulomatous tissue. This combination portrays a distinct histologic picture which clearly indicates the nature of the process and serves to classify it beyond any reasonable doubt. The foam cells are believed to be due to a faulty intracellular metabolism of cholesterol or its esters rather than to a deposit or infiltration of cholesterol from the serum into the cell for in this, as in other forms of xanthomatosis, the serum does not contain increased amounts of fats.

TREATMENT

Our experience confirms that of Sosman and others that roentgen therapy is a method of choice for the skeletal manifestations of this disease. The radiosensitivity of the bone lesions in this condition is shown by the most gratifying response of our first case, a child of 2 years, whose treated lesions included the entire spine, pelvis and upper femora, upper humeri, right seventh rib, and upper left tibia and fibula. All the lesions responded to a dose of 300 r using 190 Kv., 0.5 mm. Cu, 50 cm. TSD., and 30 Ma. of cur-

rent. This patient, closely followed for twelve years, has no symptoms or signs of this disease and there has been remarkable restoration of contour and of destroyed bone (see Fig. 329).



FIG 329. A, Hand-Schüller-Christian's disease. Note involvement of ilia and upper femora. B, Same case showing marked involvement of the thoracic and lumbar spine with extreme compression of several vertebrae. Mild roentgen therapy yielded an excellent end result.

Another most satisfactory result was obtained in a boy of 10 years whose lesions included the skull, dorsal spine, lumbar spine, and right hip. A total of 600 r was given in divided doses to each of these areas with equally gratifying bone regeneration.

EOSINOPHILIC GRANULOMA

This form of the disorder is most often seen in children and adolescents. It is uncommon and two of the largest series of cases yet reported contained but 10 cases each. While serving as surgical consultant to a Service Command we saw 2 cases among soldiers and recall a number of others in civilian practice.

While multiple lesions are described as occurring in from 20 to 60 per cent of cases of this disease, it would seem probable that the failure to



FIG. 330. Eosinophilic granuloma (diagnosis established by biopsy). *Note resemblance to osteolytic sarcoma or endothelioma.*



FIG. 331. Eosinophilic granuloma of ilium (Station Hospital, Camp Bowie, Texas)

GRANULOMATOUS DISEASES

make a roentgenographic survey of the entire skeleton may find some of the apparently solitary cases. Obviously one should not make such a complete examination when a single lesion is discovered.



FIG. 332. Eosinophilic granuloma of tibia

may be affected but in our experience the ribs, scapula, ilium, femur, and skull have seemed prone to be involved.

The symptoms are most unreliable. There may be none, or only one area of the several ultimately discovered may give rise to complaints. Local symptoms may be pain, swelling, deformity or dysfunction.

with the site and the degree of involvement. The onset is often insidious and the symptoms may have been present for a considerable period prior to the first observation.



FIG. 333. Eosinophilic granuloma of radius in a 5-year-old girl.

Moderate leukocytosis and mild eosinophilia are usually present. While some authorities assume an infectious agent as the cause of the condition, attempts to culture bacteria or viruses have yielded negative results.

ROENTGENOGRAPHIC APPEARANCE

Since the lesions are wholly osteolytic they appear as radiolucent areas of irregularly circular shape, quite well circumscribed and even punched

out. They are obviously of central rather than cortical origin and the latter is destroyed centrifugally from within by a process of erosion (see Figs. 330-335). At times the cortex may be expanded and eventually even completely perforated. In such instances reactive periosteal bone formation may be seen.

The insidious onset, the vague symptoms, the destructive bone lesion, all tend to suggest either a primary bone sarcoma or, in older patients, a metastatic cancer or plasma cell myeloma.

DIAGNOSIS

Since the condition has become more familiar it seems possible to make a pre-

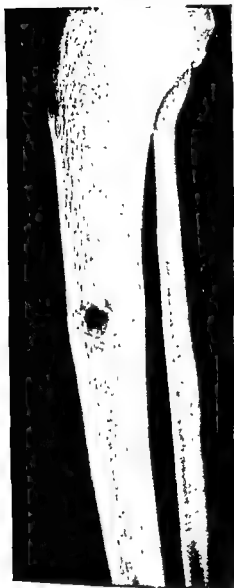


FIG 334. Eosinophilic granuloma of tibia.



FIG 335. Eosinophilic granuloma of scapula. (Brooke General Hospital, Fort Sam Houston, Texas.)

sumptive diagnosis because eosinophilic granuloma lacks the radiographic appearance characteristic of the other destructive diseases of bone (osteolytic sarcoma, Ewing's sarcoma, giant cell tumor, and simple bone cyst) occurring in the period of childhood and adolescence. The ultimate decision must, however, rest upon a microscopic study of the tissue removed by curettage. The histologic picture is typical and offers little difficulty since the tissue consists mainly of histiocytes interspersed with eosinophiles (see Fig. 336).

TREATMENT

Surgical extirpation of the affected area of bone destruction by curettage, followed by primary wound closure, suffices to promote healing and results

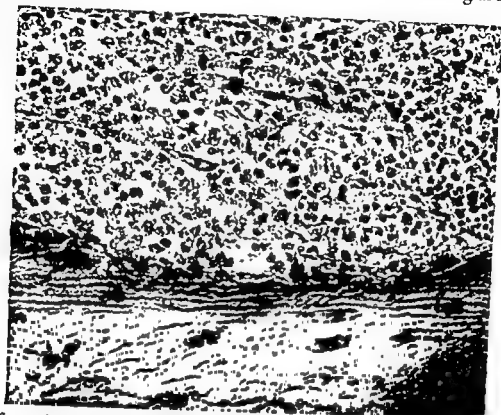


FIG. 300. Microphotograph of eosinophilic granuloma of bone. Granules in eosinophiles not visible at this magnification.

in complete cure. Mild roentgen therapy may reasonably be expected to promote resolution and is to be preferred if the lesion is in an inaccessible location (e.g., vertebra). Some evidence is available that these lesions may sometimes heal spontaneously.

64. CONDITIONS DUE TO PARASITIC DISEASE

HYDATID DISEASE OF BONE

WHILE HYDATID DISEASE IS RELATIVELY COMMON IN AUSTRALIA, ARGENTINA, China, and parts of Europe, it is comparatively rare in the United States where less than 500 cases have been reported; all but a score of these were in immigrants from countries where the disease was endemic. When it is considered that skeletal involvement is confined to about 1 per cent of all reported cases it is apparent that this form of the disease is exceedingly rare in this country. Yet because it may present roentgenographic features that resemble giant cell tumor, plasma cell myeloma, and metastatic carcinoma, it may sometimes have to be considered when lesions of bone are encountered.

Dew of Australia and Ivanissevich of the Argentine have made notable contributions to our knowledge of this disease; the latter collected all the bone cases prior to 1934 which were reported from the Argentine. The distribution is of interest because it reveals the predilection for certain bones and particularly those of the axial skeleton in contrast to those of the extremities. The bones involved were as follows:

Vertebran	14
Ilium	13
Humerus	7
Tibia	5
Femur	5
Sternum	1
Skull	1
Maxilla	1
Scapula	1
	—
	48

Only 10 cases of osseous hydatid disease have been reported in North America, by Woods, Walker and Cummins, Hines, Stone, Coley (2),

Howorth, Sinberg, Massachusetts General Hospital (case report), and Hood, Lambert, and Thomas.

Most observers claim that the vertebral column and pelvic girdle account



FIG. 337. Hydatid disease of ilium. Diagnosis confirmed by histologic examination.

for approximately half the cases. The epiphyseal region of the long bones seems to afford a site of predilection for the parasite which unquestionably is lodged there by way of the blood stream. It must first pass through two natural filters, namely, the liver, to which it comes from the intestine via the portal vein, and the lungs which it reaches after passing through the heart.

CLINICAL MANIFESTATIONS

The course of osseous hydatid disease is unquestionably of long duration; the parasite exhibits the greatest latency in skeletal tissue. The symptoms, therefore, may be very late in manifesting themselves. Pain is a late phenomenon and it usually follows some complication, such as pathologic fracture or secondary infection.

Following a pathologic fracture metastatic lesions in the lungs may develop since the opportunity is afforded for circulation of the viable elements of the organism by way of the ruptured vessels.

One of the 2 cases reported by the author complained of pain in the knee, stiffness of the hip, and, on examination, was found to have a palpable mass in the right iliac fossa (see Fig. 337). The other patient attributed his difficulties to a fall on the sacrococcygeal area, which was immediately followed by severe pain in the back radiating down the lower extremities to the knees. However, he endured these symptoms for five years before seeking hospital care. His lesion involved the left wing of the sacrum. Roentgenographically it resembled an osteochondrosarcoma.

Both of these patients presented clinical and roentgenographic features compatible with malignant disease of the pelvis; both were heavily irradi-



FIG. 338. Hydatid disease involving sacrum. Autopsy specimen.

ated. Aspiration biopsy finally furnished the clue by which eventual histologic confirmation was obtained in the first case; in the second, the diagnosis was not established until autopsy was performed (see Fig. 338).

ROENTGENOGRAPHIC APPEARANCE

It has always been difficult to make a roentgenographic diagnosis of hydatid disease for the bizarre picture may be similar to that of osteomyelitis, metastatic malignant disease, myeloma, or even chondromyxosarcoma.

The treatment of osseous hydatid varies considerably according to the location of the lesion and the degree of bone involvement but on the whole therapy is difficult and its results often discouraging. Curettage has been employed successfully in some instances supplemented by the use of a cauterizing agent such as phenol or formalin, but this method is condemned by Dew as "always unsatisfactory and, even if carried out thoroughly . . . unlikely to succeed." Complete resection of the involved segment of bone followed by immediate reconstruction with an autogenous bone transplant is suitable in certain cases involving long bones and has been used successfully in the ilium (Finochietto). Complete extirpation of the humerus has been performed by San Martin and Valdez, Arce and Ivanisovich, and by Gernez. A fairly satisfactory functional result was obtained by the use of suitable prosthetic appliances. Total excision is also suitable in cases involving the scapula, clavicle, and rib.

Widespread lesions with marked destruction of the soft tissues or extension into neighboring joints may present the indications for amputation or disarticulation. When the pelvic girdle is totally involved the results of treatment are more discouraging. Loucks expresses the view that "the only hope seems to lie in the discovery of some anthelmintic drug which, when administered by the intravenous route, will have a specific lethal effect upon the echinococcus organism."

Owing to the fact that the organism develops in such a slow and symptomless manner, a pathologic fracture is frequently the first manifestation that calls the patient's attention to the lesion. The delay in the recognition of the disease is one of the chief reasons why the prognosis is ultimately so discouraging. D  v  , Billiard, and Decoular  -Delafontaine, after experiments on infested animals, consider that deep radiation therapy has no effect on the cysts. The ideal therapy—complete extirpation—while adapted to certain visceral cases, affords extreme difficulty in a case of hydatid cyst of bone. Amputation may give an excellent prognosis in cases where it is rendered necessary because of the extent of bone destruction.

The 2 cases personally observed lend strong support to these views, especially as regards the ineffectiveness of deep radiation therapy.

65. CONDITIONS DUE TO DISTURBANCES OF BLOOD SUPPLY

ASEPTIC NECROSIS OF BONE, CAISSON DISEASE

AMONG THE UNUSUAL CONDITIONS THAT MUST BE CONSIDERED AS A POSSIBLE cause of vague bone and joint pain is aseptic necrosis with bone infarction. Any interruption of the nutrient vessels to a segment of bone may result in infarction of that segment. When this occurs in the absence of infection the necrotic area gradually heals; if the lesion is small it may leave no trace, but it usually results in a hypercalcified appearance which presents a characteristic roentgenographic picture. Because these areas are so seldom seen they may be confused with a sclerosing bone tumor, such as a sclerosing osteogenic sarcoma.

ETIOLOGY

While local acute trauma or embolism by a small blood clot may conceivably interrupt the continuity of the nutrient artery, the most frequent cause of aseptic necrosis is embolism from nitrogen bubbles consequent to rapid changes in atmospheric pressure. Therefore, as would be expected, the condition is seen in divers, "sand hogs," and others working under altered atmospheric pressures. While little information is available, it seems probable that it would also affect combat pilots making rapid ascents to high altitudes.

The amount of air which will dissolve in blood is proportional to the atmospheric pressure. When the pressure decreases suddenly the dissolved air is released from solution in the form of bubbles. Only one-fifth of the air is oxygen, and oxygen is readily taken up by tissues and red blood cells so that changes in oxygen pressure cause little damage. Nitrogen, on the other hand, constitutes four-fifths of the atmosphere and is physiologically inert. When nitrogen bubbles form in the blood owing to sudden reduction in atmospheric pressure they are not metabolized but are trapped in the small vessels and give rise to infarcts. In bone, where blood supply is poor and anastomoses infrequent, areas which had been supplied by the infarcted

vessels receive inadequate nourishment from the feeble collateral circulation and become necrotic.

LOCATION OF BONE AND JOINT LESIONS AND THEIR RELATIONSHIP TO EACH OTHER

The favorite site for both symptoms and lesions is the long bones. Due possibly to the high proportion of red as compared to fatty marrow, the vertebrae and membranous bones escape. Erdman reports about 70 per cent of symptoms in the lower extremities, chiefly the knees, the remainder being in the upper extremities. These figures coincide with those of other authors. Erdman also states that he aspirated under water a few cubic centimeters of gas from beneath the periosteum of the tibia of 2 workers.

The location and severity of symptoms depend upon the site and volume of gas set free; pain results when it is confined beneath any unyielding tissue, such as muscle bundles, ligaments, fascia, periosteum, and nerve sheaths. Symptoms are rare in the liver, spleen, kidney, fat deposits, or veins. These latter "silent" areas outnumber the "painful" ones, which in turn outnumber the "vital" ones, such as the central nervous system. Symptoms have occurred during decompression but are most common during the first few minutes after decompression. Reexposure after incomplete decompression is known to predispose to attacks, as is the use of alcohol shortly prior to exposure.

German authors described 11 cases, all of which presented lesions involving a large joint. The hip was affected 12 times and the shoulder once. All cases, with two exceptions, were monoarticular; both exceptions were bilateral in the hips. These authors agree with Phemister, Kahlstrom, and Burton that the pathology is a result of nutritional interference either from direct embolism in a main nutrient vessel or of pressure on the vessel wall by bubbles, or both. This sets up a train of infarction plus aseptic necrosis of varying extent. Following this is the classic picture of gradual attempts at repair on the part of the bone by osteoclasia, creeping substitution, and eventual delimitation by calcification as described elsewhere. The German authors mentioned are of the further opinion that the characteristic picture of alternating areas of translucency and density, with a secondary arthritis, is not the result of one exposure but rather of repeated insults. All agree that the arthritis, which is of the deforming type, is a result of absorption, collapse, and new bone formation in or near an epiphysis. Only one pathologic specimen was examined by them, and that only in the gross, the head of the femur and capsule being described as having many knobby excrescences. The German authors make no mention of extensive areas of aseptic necrosis extending far along the shafts of the long bones from the initial diaphyseal lesion. The vessels in this region have few anastomoses and are therefore easily clogged, which fact probably influences the loca-

tion of the lesion. They are usually limited to the regions near the ends of the long bones; the midshaft is seldom affected.

ROENTGENOGRAPHIC APPEARANCE:

The importance of recognizing both the clinical and roentgenographic features of this disease, in view of its intimate relationship to possible compensation claims, is self-evident. There is 1 case recorded of arthritis deformans of the hip allegedly resulting from caisson disease, in which the causal relationship was not established and compensation was denied (Jaeger). Aside from the purely legal aspects, this apparently was adjudged chiefly on the grounds that it was an occupational disease and did not occur as the result of one attack. Also, the first signs were noted three years after the exposure and came on intermittently. No roentgenograms of the long bones were thought to be consistent with early deforming arthritis, although one expert considered it to be caisson disease. The medicolegal aspects of this condition have been emphasized in recent years with the appearance of several claims under workmen's compensation laws of New York State. These workmen, at one time employed as divers or caisson laborers, developed deformities in weight-bearing bones, notably the hip, as a late result of the softening in infarcted areas which induced deforming arthritis. It is considered probable that in the future these bone and joint lesions will come to be regarded as industrial diseases and that compensation will be awarded in suitable cases. However, Taylor has pointed out that exactly similar alterations of bone have occurred in persons who have never had occupational or other exposures to compressed air; in fact, in his series of 54 cases of bone infarct with aseptic necrosis less than a third had a positive history of exposure.

Other conditions that have been found in association with bone infarction are sickle cell anemia and rheumatic fever, but the exact mechanism of the interference with circulation in these and other nonatmospheric cases remains conjectural.

Roentgenographically, caisson disease may be distinguished by multiple distribution in the medullary portion of the bone; it rarely, if ever, produces cortical change. The shaft is not expanded and the infarction presents an area of irregularly increased density usually surrounded by a thin band of calcification, on the outside of which is a variable amount of normal-appearing medulla. The lesion is located in the diaphysis and may or may not involve the epiphysis and secondarily the joint. Articular changes resemble arthritis deformans. The lesions almost always are located in the large long bones, i.e., the femur, tibia, and humerus, and are more often in the lower than in the upper extremity (see Figs. 339-341).

In making a diagnosis, the diseases most likely to be confused are: (1) *chronic sclerosing osteitis*, which is not usually multiple and in which there



FIG. 339. A, Caisson disease (aseptic necrosis of bone) showing characteristic medullary infarct of femur. B, Lower tibial involvement in the same case showing evidence of bone infarct.

eliciting a history of patients with lesions of bone or joints suggestive of infarction and aseptic necrosis, one should remember to inquire as to previous occupational exposures to extremes of atmospheric pressure, at the



FIG 341. Metastatic carcinoma of renal origin arising in an area previously the site of aseptic infarct in a caisson worker. *Note* the area of bone destruction due to carcinoma superimposed on sclerotic changes due to the infarct.

same time realizing that a negative history of such exposure by no means precludes the possibility of the lesion being one of aseptic necrosis.

James has recently described cases of bone lesions occurring in submarine personnel who had escaped from a submarine sunk in 120 feet of water. Five of the survivors were examined after twelve years had elapsed and of these three showed bone lesions. These are apparently the first cases to be described in Navy personnel.

It appears from early reports that there are far fewer cases in flying personnel of the Air Corps than might have been anticipated. At the School of Aviation Medicine at Randolph Field the hip joints were studied of 21 subjects intermittently exposed to simulated altitudes of 35,000 feet or higher in the low pressure chamber. The total duration of exposure for each

individual was from five to one hundred hours. However, it was recommended that these studies be repeated after several years to determine whether detectable lesions had developed with the passage of time.

The time factor may perhaps explain why in the low pressure chamber individuals did not develop bone lesions commonly seen in caisson workers. When one gets the bends in the low pressure chamber he is immediately recompressed by "dropping" the lock or chamber to lower altitudes, yet it may be minutes or even hours before the caisson worker can be recompressed since his symptoms may not come on until he is some distance from a recompression lock. The duration and frequency of exposure of caisson workers may be a factor explaining why lesions of bone are more common in them.

LOCALIZED AREAS OF CALCIFICATION IN CANCELLOUS BONE

Small irregular areas of amorphous calcific deposition in bone have been infrequently described. While in most respects these areas bear a close resemblance to the more extensive ones seen in the infarcts of caisson disease, they are found in persons who have never been exposed to the atmospheric pressure changes which are responsible for the lesions seen in caisson workers.

The site of predilection is in the spongiosa near the metaphysis of long bones. The bone is not expanded, the cortex is uninvolved and the condition does not give rise to any symptoms. Consequently it is discovered in the course of a roentgenographic examination made because of some other complaint, usually related to the adjacent joint.

Ferguson has given the only extensive account of this entity and reported on 42 examples. He observed their frequency in areas of greatest skeletal growth with approximately 60 per cent situated in the distal end of the femur. In the vast majority of cases the lesion is solitary. With a single exception, all of the patients were 40 years of age or more. In those cases in which serial roentgenograms were made over periods ranging from six months to two years no changes in the appearance of the process were observed.

Ferguson was able to study microscopic sections from one of these areas removed in the course of an operation for an unrelated condition. The lesion consisted of calcified, nonviable cartilage which at its periphery showed some new bone formation. These findings inclined Ferguson toward the theory that the lesion is one of the many forms of chondrodysplasia. Yet because there is no evidence that it possesses any potentialities for autonomous growth he regards it not as an enchondroma but rather as a degenerated island of calcified cartilage which failed to progress to complete ossification at the time of skeletal growth. Trauma and rickets have also been mentioned as potential etiologic factors. The author considers it entirely

possible that the process is merely the result of a small bone infarct which produces a localized area of aseptic necrosis with late secondary calcification.



FIG. 342. Calcinosis. The condition was bilateral and there were associated varicosities.

Mention is made of these calcified medullary defects because they may present a superficial resemblance to sclerosing osteogenic sarcoma, osteoid osteoma and, occasionally, to osteoblastic prostatic metastases. Osteogenic sarcoma of sclerosing type is associated with pain and there is also involvement of cortical bone and usually definite evidence of destruction as well as sclerosis. Osteoid osteoma is accompanied by extensive reactive new bone formation rather than calcification and a central radiolucent area, the nidus, is usually apparent. Prostatic metastasis to bone is seldom confined to a single area and is rare in the areas where localized calcification in cancellous bone is most often found. It should not be difficult to decide which of the two conditions is present after skeletal scout films have been made and serum alkaline and acid phosphatase levels have been determined.

Since these calcified medullary defects are symptomless and innocuous no form of treatment is required.

CALCINOSIS (CHALK GOUT)

This condition is principally manifested by depositions of calcium in varying amounts in the skin and subcutaneous tissues. It occurs in several



FIG. 343. Calcinosis, circumscribed form. Shows typical distribution in fingers and on extensor surfaces of elbows.

forms variously described as *calcinosis conscripta*, *calcinosis universalis*, *tendino-fasciitis calcarea rheumatica*, *Raynaud's disease with calcareous degeneration*, and *tumoral calcinosis*.

The universal type, generally occurring in the first two decades, involves extensive portions of the skin and subcutaneous tissues and sometimes the interstitial tissue of tendons, nerve sheaths, muscles, and fascial planes. It has an unfavorable prognosis. No form of therapy has been successful (see Fig. 342).

The circumscribed form is seen more often in the female and in older patients. It is restricted to the region about the terminal phalanges and the extensor surfaces of elbows and knees. It may be associated with Raynaud's disease, scleroderma, and sclerodactylia (see Fig. 343).

The massive or tumoral form described by Inclan of Havana concerns us more than do the others, since at first glance it may closely resemble a bulky, sclerosing tumor of bone.

ETIOLOGY

No conclusive evidence exists to point to the exact pathogenesis of calcinosis. One theory implies an altered calcium metabolism but no cases have been observed in which this is indisputably shown. The other theory, equally unproved, maintains that calcium deposits occur in connective tissue that has become degenerated.

TUMORAL OR MASSIVE CALCINOSIS

Inclan encountered 3 cases, all occurring in Negroes, whose lesions had a marked resemblance and were dense tumors of large size. The gluteal

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TUMORAL OR MASSIVE CALCINOSIS

Inclan encountered 3 cases, all occurring in Negroes, whose lesions had a marked resemblance and were dense tumors of large size. The gluteal

and iliac region was affected in 2, while in the remaining case the elbow region was bilaterally involved. This form of calcinosis seems quite distinct and does not closely resemble the other types. Since it alone seems likely to be confused with bone tumor, it will be described in some detail.

Clinical Manifestations of Tumoral Calcinosis

Two of Inclan's cases had pain; all complained of the presence of a swelling. Trauma was a possible etiologic factor in 1 instance. None of the cases showed evidence of calcifications elsewhere in the body although the elbow case later developed a similar swelling on the opposite elbow. Joint involvement was lacking and blood-chemistry studies were not unusual except for an elevated cholesterol in 1 patient.

Striking characteristics were the large size of the swelling, its origin in the region of the bursa, and its spread far beyond the confines of bursal structures into adjacent and ultimately distant muscle groups. Radiographic examination revealed a massive, extremely dense spheroid or ovoid tumor mass which, on a single film, could not be distinguished from a dense calcified osteoma or a sclerosing osteogenic sarcoma. Views from several angles might have been helpful and it is possible that stereoscopic films would have disclosed the fact that *the bone was not involved*, the process being wholly confined to the soft tissue.

Biopsy of these tumors revealed the presence of many cavities filled with a milky, thick fluid which was found to be calcium carbonate in suspension and to have a high albumen content. Cultures were uniformly sterile. Animal inoculations gave negative results. Microscopic sections showed the tumor to be composed of large calcareous deposits within a fibrous trabeculated meshwork. Where the trabeculae were thin, hyalinization was seen. Foreign-body type giant cells were numerous.

This clinical entity seems to differ from types of calcinosis described by Steinitz and others (calcinosis circumscripta and calcinosis universalis) and from Virchow's metastatic calcinosis. Inclan believes it probable that the process originates in bursae and spreads to involve muscle.

Inclan's cases suggest that surgical extirpation is the method of choice wherever feasible but that incomplete removal will probably be followed by the development of another tumor. Observation over a period of many years is necessary before the entire cycle of this condition can be fully understood. Inclan used high-voltage roentgen therapy postoperatively on 1 of his cases with no demonstrable effect.

Treatment

Rothstein and Welt have pointed out the ineffectiveness of medical treatment of calcinosis with preparations of parathyroid, acetylcholine, insulin, pilocarpine, and of physical therapy, heliotherapy, roentgen ther-

apy, and even surgery. Ramsdell's recent report of cases treated by hemithyroidectomy and parathyroidectomy indicates that great improvement resulted. His cases were apparently of the type described as *calcinosis universalis*. It is not clear how parathyroidectomy would be of benefit unless the chemical studies of calcium, phosphatase, and phosphorus showed evidence of hyperparathyroidism. Byron and Naicholover, however, reported a case of *calcinosis universalis* with scleroderma and sclerodactylia with normal calcium metabolism, in which removal of two parathyroids, histologically identified, had no effect on the calcium deposits.

CASE REPORT*

Mrs. T.S.G., aged 45, of Austrian extraction, was admitted to Memorial Hospital on May 2, 1941. At the age of 10 she had sustained a fall which was followed in a short while by swelling on the inner aspect of the left knee. This caused little discomfort and no medication was required. For the next thirty-five years the swelling slowly increased in size and for the past ten or twelve years there had been some pain in the knee region, present only during the night. For the past three or four years the knee has been stiff enough to cause her to walk with a limp. The patient was the mother of five children and was able to work as a janitress with very little disability. Ten years ago, on account of the pain, a radiographic examination was made and an operation advised but this was refused. At this time a swelling was noted over the anterior tibial region on the left side and a mass in the left inguinal region which she thought was a hernia. Five years later a small mass appeared over the inner aspect of the left foot. Later the pain became sufficiently severe to prompt her to seek medical attention.

Description of tumor: with the exception of the left lower extremity there was nothing remarkable about the physical examination. There was a bone deformity of the pubic portion of the left ilium and upper femur with limitation of abduction, rotation, flexion, and extension at the hip. The circumference of the left knee measured 50 cm. Over the inner aspect of the knee was a hard nodular swelling measuring 23 x 26 cm. It seemed to be attached to the upper portion of the tibia and the lower portion of the femur and to be arising from the knee joint. There was some increased local heat. The patella did not appear to be involved. There was a fusiform enlargement of the midportion of the left tibia and a nodular, firm, semi-elastic swelling over the inner aspect of the left foot which did not appear to interfere with the function. The roentgenographic find-

* The patient was readmitted to Memorial Hospital for operation on Nov. 24, 1947, after the above case history had gone to press. Extensive incisions were made and the large masses in the thigh and about the ankle were dissected out and excised. The gross findings of the pathologist indicated that these masses were entirely surrounded by irregular fat and muscle tissue. His report states: "In the center and making up a large portion of the specimen there are bony hard masses which when cut by a power saw present a very hard surface appearing like bone cortex. . . . All of these specimens are intimately connected with firm, yellowish-white, connective tissue and adipose tissue." The microscopic study was reported to show osteochondroma and . . . a unique case of multiple extraskeletal osteochondroma. The patient made a satisfactory recovery and when last condition with good function of the extremity.

ings are clearly shown in Figure 344. A surgical biopsy was performed in May, 1941, and a wide excision of the tumor about the knee was done in July, 1942. The biopsy specimen showed dense bone with well-developed haversian systems

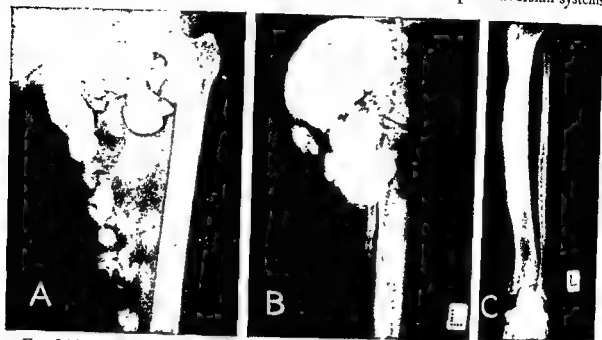


FIG. 344. Roentgenographic appearance of a most unusual case with marked involvement of soft tissue by dense masses which were excised and proved to be osteochondromas. A demonstrates the extensive deposits in the soft parts of the upper thigh. B, Appearance of the mass about the knee. C, Note the changes in the tibia strongly suggestive of melorheostosis. A unique case which was first regarded as an example of tumoral calcinosis.

without any suggestion of a neoplastic process. The second specimen consisted of numerous globoid fragments measuring from 4 to 11 cm. in diameter. All of the tissue was extremely firm, rocklike material resembling bone. The specimen was lost or mislaid before a microscopic examination could be made.

The chemical constituents of the blood revealed normal levels for phosphatase, phosphorus, and calcium, and the blood count was not remarkable. In the three and one-half years following the attempted excision of the tumor about the knee the patient was relatively free from symptoms and examination revealed no significant change in the local condition throughout the extremity. During a period of twenty-five years there is no record of a similar case at Memorial Hospital. The interesting features are the multiplicity of lesions, the long duration (thirty-five years), the comparatively slow growth rate, the resemblance to masses of calcium as seen in the roentgenograms and the similarity to Inclán's cases reported as *tumoral calcinosis*, and finally, the apparently unassociated changes in the left tibia which bear a close resemblance to melorheostosis.

When seen on Feb. 21, 1946, the patient was still comparatively comfortable and roentgenograms failed to reveal any remarkable change when compared with others made shortly after the operation in July, 1942.

66. CONDITIONS DUE TO TRAUMA

MYOSITIS OSSIFICANS (OSSIFYING HEMATOMA)

AN IMPORTANT BENIGN CONDITION OF THE MUSCULOSKELETAL SYSTEM which requires consideration in any discussion of bone neoplasms is that of myositis ossificans traumatica. It may be described as a reaction of certain tissues to trauma characterized by a deposition of bone in the periosteum, muscles, and in the sheaths of tendinous insertions of muscle to bone. Several forms of the disease are recognized. The more common variety, myositis ossificans circumscripta, is localized to a single muscle group and usually has its inception in a single trauma. The comparatively rare and progressive form, myositis ossificans progressiva, usually terminates fatally. It generally commences in the muscles attached to the spine and extends gradually to involve those of the entire body.

Rosenstern cites Guy Patin as having reported the first case when in 1692 he described the woman who turned to wood. Similar cases were reported by Freke (1740) and Copping (1741). In 1860 Bulhak was the first to point out that there were two forms of myositis ossificans. Von Dusch in 1868 gave the disease its name.

The localized form is the one which is of particular interest to the oncologist for it may be the source of great anxiety owing to its close resemblance to periosteal osteogenic sarcoma from a clinical, roentgenographic, and microscopic viewpoint. This similarity has been known to result in diagnostic errors responsible for unnecessary amputations.

ETIOLOGY

Trauma due to a single or repeated blow or fall is the generally accepted inciting factor. The so-called "charley-horse" of athletic injuries is a typical example. When the injury causes a hematoma involving stripped-up periosteum and contused overlying muscle, conditions are ideal for the development of myositis ossificans; this may be explained as aberrant osteogenesis.

On the other hand, when the periosteum is not injured its development is explained as due to metaplasia of connective-tissue cells. Heredity has been offered as a predisposing factor but there is little to support this theory.



FIG. 345. Ossifying hematoma following local injury.

Systemic changes have also been considered as playing a part in its development but in cases in which the chemical constituents of the blood have been determined they have been normal. Hormone abnormalities are notably absent. Age is probably not a direct factor, although, owing to the fact that injuries are more common in youth and young adult life, the majority of cases are found in these periods. Males are more often affected than are females and for a similar reason.

The favorite sites are the thigh, elbow, and shoulder regions; the muscle groups most often involved are the quadriceps, adductor, brachialis anticus, and deltoid regions. Those which are found about the elbow are usually associated with fracture dislocations.

CLINICAL FEATURES

Following closely upon the injury, a mass develops which is firm and somewhat tender, and which gradually increases in size although it may have reached its peak when first noted. Its consistency later becomes as hard as that of bone, this transition requiring several weeks to a month. Thereafter it remains stationary and may even decrease somewhat in size and, on rare occasions, may disappear almost completely. Pain is notably absent after the

effects of the original injury have subsided.

ROENTGENOGRAPHIC APPEARANCE

Immediately following the injury the roentgenographic findings are negative (unless there has been an associated fracture). Within one to

three weeks evidence of early osteoblastic activity will appear on the films and it is at this stage that the roentgenologist may find it extremely difficult to state whether or not he is dealing with a true bone-forming sarcoma.

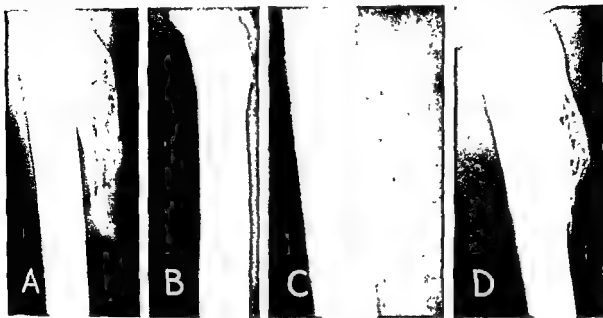


FIG 346. A, Ossifying hematoma, following an injury. B, Appearance after operative removal. C, Showing recurrence after removal. D, Final appearance. This case illustrates tendency of the process to recur after removal, especially when undertaken early.

When first seen some months or more after the injury the orderly contour of the process is so characteristic that there should be no difficulty in correct interpretation (Figs. 345-348).

BIOPSY

In trying to decide on a diagnosis of sarcoma or myositis ossificans one should never rely entirely upon an aspiration biopsy for even with plenty of material obtained from an exploratory operation the pathologist may find it difficult to reach a decision.

The gross appearance at operation is also confusing, for a mass of fleshy, tumorlike tissue is found which may closely resemble sarcoma invading muscle. Attachment to periosteum and in turn even to bone itself further tends to mask the nature of the process.

Microscopic sections disclose islands of cartilage, spicules of newly formed bone, myxomatous areas, calcified connective tissue, and areas of degenerating muscle fibers. This picture has misled some of the most experienced pathologists to decide on a diagnosis of sarcoma (see Fig. 349).

DIFFERENTIAL DIAGNOSIS

Although at times a correct diagnosis may be comparatively simple, under certain circumstances it may be a matter of great difficulty. We have found the following points to be helpful:



FIG. 347. Myositis ossificans.



FIG. 348. Myositis ossificans in a cowboy. Note the bilateral lesions in the adductor regions. (U. S. Signal Corps.)

MYOSITIS OSSIFICANS

Trauma nearly always precedes the discovery of the tumor and the interval is brief.

The symptoms are comparatively mild, and pain is seldom complained of while the part is at rest.

Stereoscopic films reveal an intact cortical line and show that the process does not invade or destroy bone.

Microscopic sections fail to disclose evidence of cellular atypism.

OSTEOGENIC SARCOMA

Trauma may be claimed as an antecedent factor but the tumor seldom appears within so brief a period after injury.

Pain usually precedes the discovery of the tumor, is worse at night, and increases in severity.

Stereoscopic films demonstrate clearly that the bone is actually affected.

Microscopic sections may reveal cellular atypism in varying degree. When this is lacking the pathologist can assure a relatively lowgrade tumor in which a short delay for further clinical and roentgenographic observation is justifiable.

If, after weighing all the evidence, doubt of the diagnosis still exists, one is justified in adopting a policy of observation at frequent intervals with weekly recheck of the roentgenographic findings. Within a period of three or four weeks a correct decision can usually be reached; this is based on the gradations of change in the appearance of the films, the continuing absence of pain, and the failure of the swelling to increase in size. This is one condition in which the film is generally more dependable for the diagnosis than is the microscopic section. Especially is this true in cases intimately associated with the bone and periosteum. In other rare instances where the process lies wholly within the muscles a correct diagnosis is not apt to be so difficult.

SARCOMA DEVELOPING IN MYOSITIS OSSIFICANS

One of the rarest examples of the late transition of a benign bone lesion into a malignant one is the development of osteogenic sarcoma in an area of ossification caused by myositis ossificans. Shipley (1940) reports that only 4 cases had previously been found in the literature. Butler and Wooley described the development of an osteogenic sarcoma in a calcified hematoma in a woman of 68. Pack and Braund added 2 cases in 1942; 1 concerned the evolution of a sarcoma sixteen years after the occurrence of an ossifying hematoma; their second case is not so convincing an example of sarcoma arising on a basis of preexisting myositis ossificans.

The author has observed only 1 unquestionable case of this type although in 2 other instances fairly convincing evidence was present which might permit of their being included.

FATIGUE FRACTURE (MARCH FRACTURE)

Passing mention should be made of the occasional occurrence of fatigue fracture in which during the early reparative phase a suspicion may be



FIG. 349. Microscopic appearance of ossifying hematoma (myositis ossificans). Note the resemblance to osteogenic sarcoma. In the early stages this condition is difficult to differentiate from osteogenic sarcoma microscopically.

raised that the condition is a primary bone sarcoma. This type of fracture is rare in times of peace but during the Second World War it was not an uncommon finding among the large numbers of recruits undergoing basic military training. It affects the metatarsal bones, particularly the second and third, in the vast majority of cases, although the tibia, femur, and even the pubic bone are at times involved. It is such cases that may arouse suspicion of malignant disease since sarcoma of the metatarsal bones is a rare occurrence (see Fig. 350).

SYMPTOMS AND ROENTGENOGRAPHIC FINDINGS

Mild pain on weight-bearing is the only symptom complained of. There is usually a history of long marching with heavy equipment. Roentgenographic examination discloses a fine—at times almost imperceptible—trans-

verse crack across the bone without any displacement. Two or three weeks later proliferative changes at the fracture site are evident and it is in this early reparative stage that a sarcoma may be simulated (see Fig. 351). As



FIG. 350. March fracture of femoral neck. This patient was never immobilized and continued to bear weight. The fracture healed with slight coxa vara. (Station Hospital, Camp Wolters, Texas.)

healing progresses the picture resembles callus as in any simple fracture, and eventually the normal appearance of the bone is restored.

"GREENSTICK" FRACTURE (SUBPERIOSTEAL FRACTURE)

Although it is quite unusual for a "greenstick" fracture to simulate bone sarcoma we have encountered several examples in which the diagnosis was difficult to make. One of these concerned a young girl who had injured the lower end of the fibula; when the first roentgenograms were made some ten days later the findings prompted the roentgenologist to suspect a Ewing's sarcoma. On our first examination at Memorial Hospital it was difficult to reach a decision but it was felt that a period of observation and a reexamination of films made after an interval of several weeks were justified before subjecting the patient to a biopsy. Subsequent roentgenographic findings showed no further progress of the lesion but rather an improvement so that a further delay seemed indicated. By this time it was apparent that we were dealing with a reparative process in an unsuspected, incomplete fracture which was made more pronounced by the fact that the patient had been walking on the extremity constantly since the injury.

In such cases the history of an injury is important and stereoscopic spot films are of great value in determining the absence of any irregular bone destruction.

PRODUCTIVE BONE CHANGES ATTRIBUTABLE
TO LOCALIZED PERIOSTEAL TEARS

When a severe trauma results in a tearing or a splitting up of periosteum



FIG. 351. Fatigue fracture (March fracture) of upper tibia. The bone proliferation associated with repair could be confused with early osteogenic sarcoma.

over a circumscribed area of bone, without producing a fracture, there occasionally develops an osteoblastic formation which may lead one to suspect the presence of an early sarcoma of bone. We recall such a case in the lower tibial region of a boy whose leg was run over by an automobile without resulting in a fracture. The subsequently developing bone changes, as described, caused anxiety on the part of the roentgenologist and the clinician. It requires fortitude to withhold surgery and to insist merely on very close observation, as a result of which course the true nature of the lesion soon becomes apparent. If, however, after a careful survey, reasonable doubt still exists, it seems justifiable to perform a biopsy without further delay and to secure histologic proof of the nature of the lesion.

67. CONDITIONS DUE TO ENDOCRINE DISTURBANCES

HYPERPARATHYROIDISM (RECKLINGHAUSEN'S DISEASE—OSTEITIS FIBROSA GENERALISATA)

THE DISEASE WHICH WE NOW RECOGNIZE AS DUE TO ABNORMAL ACTIVITY of the parathyroid gland or, more specifically, to excessive secretion of its hormone, parathormone, was first clearly described in 1891 by Recklinghausen, although Hirschberg had recognized it five years earlier and considered it a variety of osteomalacia. Recklinghausen reported 3 cases, suggested the term *osteitis fibrosa cystica*, and described the pathology of the bone changes.

Since 1907, when Erdheim recorded his studies of the parathyroids in 7 cases of puerperal and senile osteomalacia and found gross enlargement of these glands in 2 instances, the literature has contained many reports of enlargement of the parathyroids associated with diseased conditions of bone.

Dawson and Strothers, in 1923, reported a case of generalized osteitis fibrosa with an adenoma of the principal cells of the parathyroid gland. Mandl, in 1926, found that marked clinical improvement followed removal of a parathyroid adenoma with multiple osseous lesions, and was the first to prove that these bone changes were caused by perverted parathyroid function. Collip and Hanson, using preparations of active extract of the parathyroid glands, facilitated extensive studies of its effect on calcium metabolism.

The relation of this disease to the hypersecretion of the parathyroid gland is now fully established.

CLINICAL FEATURES

Uncomplicated cases prior to the advent of fracture may exhibit no symptoms. Softening of the bones, especially of the lower extremity, may cause deformity. This may attract the patient's attention and may be the

NEOPLASMS OF BONE

only symptom cited. However, unexplained fatigue, polyuria, weakness, and vomiting may be complained of.

If present at all, pain is apt to be mild and intermittent in character,

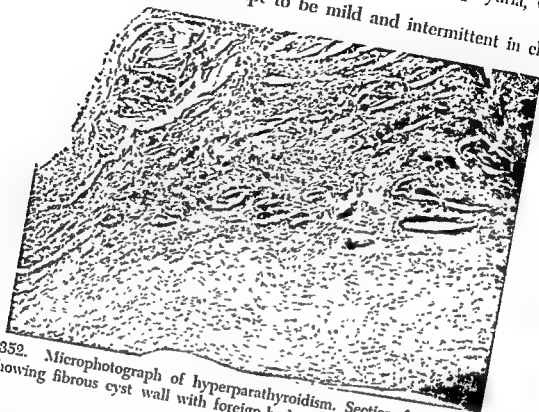


FIG. 352. Microphotograph of hyperparathyroidism. Section from cystic area in femur showing fibrous cyst wall with foreign-body giant cells, reacting to crystalline material.

resembling myalgia or rheumatoid arthritis. Fracture, however, often leads to the establishment of the diagnosis since it prompts the taking of roentgenograms which in turn leads to a study of the remainder of the skeleton. Once the diagnosis has been suspected, chemical studies of the serum calcium, phosphatase, and inorganic phosphorus will generally confirm it. The finding of a palpable tumor in the thyroid region lends further support to the diagnosis and if the pathologist reports the excised tumor to be a hyperplastic parathyroid the diagnosis may be regarded as established. Absence of a palpable swelling in the neck does not preclude a diagnosis of hyperparathyroidism for in many instances the tumor has been revealed only after several explorations. In some cases the tumor has been located subinternally in the superior mediastinum. The hypercalcemia, which is the essential derangement in this disease, is often the cause of renal calculi and a scout film of the kidney region should be made a part of the routine roentgenographic examination. In addition, there is apt to be hypophosphatemia, elevation of serum alkaline phosphatase, and increase in urinary calcium and phosphorus, these complete the chemical syndrome.

In long-neglected cases, especially those which occurred prior to our

knowledge of the cause of the disease and the consequent surgical attack upon it, death has resulted, thus ending a course marked by severe pain, multiple fractures, secondary anemia, malnutrition, impaired renal function, and emaciation. Modern methods, however, including roentgenographic examination and laboratory studies of the blood chemistry, have made it possible to arrive at an *earlier diagnosis before irreversible damage* has been done.

While decalcification and resorption of bone are the striking features of this disease; new bone is formed and pathologic fractures may generally unite (see Fig. 352). Loss of calcium may cause tenderness in the bone, followed by swellings which are usually single and asymptomatic at first but which become numerous and painful as the disease progresses. The earliest symptoms may be a pathologic fracture which is usually caused by a trivial injury. Bending of the softened bones gives rise to curvature of the spine, deformities of the thorax, pelvis, extremities, and even cranial enlargement which may or may not be symmetrical. Vertebral changes result in "fish-type" vertebrae and sometimes in a loss of many inches in height. Calcium in the teeth is apparently not affected by the hormone so that dental decalcification is not seen. This results in a striking contrast in the X-ray film, the teeth standing out prominently as compared to the malacic alveolar bone.

SKELETAL MANIFESTATIONS

Roentgenographic study of the bones reveals marked individual variations in the location, extent, multiplicity, and roentgenographic appearance of bone lesions. Since an *earlier diagnosis is now being made in this disease*, which is insidious in its onset and often slow of development, the advanced appearance in which cysts and giant cell tumors are seen is now much less frequently observed.

In the early stages a decalcification that produces a granular miliary mottling is noted, especially in the skull and flat bones. In a tubular bone the normal trabeculae become indistinct and the cortex is thinned. The process is one of osteoporosis which may later be associated with cysts or tumors containing giant cells. As the cortical thinning progresses, pathologic fracture becomes a fairly common complication; such fractures tend to heal. In advanced cases the metatarsal and metacarpal bones, and even the phalanges, may develop cystlike changes (see Figs. 353 and 354).

LABORATORY FINDINGS

There is an elevation of the serum calcium varying from 12 to as high as 23.6 mg. per cc. The average is 14 to 16. Serum phosphorus is decreased

to 1 or 1.50 mg. per 100 cc. Serum alkaline phosphatase is increased to from 12 to 20 Bodansky units. There is no more important corroborative evidence in favor of this disease than that afforded by these findings.



FIG. 353. A, Hyperparathyroidism. Note the marked osteolytic changes in the ilium, ischium, pubis, and upper femur.

CLINICAL TYPES

Of the 6 clinical types of hyperparathyroidism described by Albright, Aub, and Bauer, 2 are concerned with changes in the appearance of the bones. These are:

Type 1: classic Recklinghausen's disease with skeletal symptoms and signs predominating—decalcification, cysts, tumors, and pathologic fractures:

Type 2: osteoporotic form—characterized by generalized demineralization but without cystlike areas or tumors. This latter group undoubtedly represents an earlier and less advanced form of the disease.

DIFFERENTIAL DIAGNOSIS

Under certain conditions the diagnosis of Recklinghausen's osteitis fibrosa may involve a differentiation from the following:



FIG. 353 (continued). B, Hyperparathyroidism showing involvement of the ribs and vertebral bodies.

1. Malacic diseases, such as osteomalacia, osteoneuropathy (renal rickets), senile osteoporosis, or Paget's disease
2. Locally destructive but benign lesions, such as fibrous dysplasia of uncertain etiology, solitary bone cyst, or giant cell tumor
3. Malignant diseases with widespread bone involvement, such as plasma cell myeloma, or metastatic carcinoma

This problem of differential diagnosis is simplified by the fact that in none of these other conditions is the serum calcium elevated to levels consistently above normal. Moreover the roentgenographic changes are dissimilar. Giant cell tumor is almost never multiple, hence a suspected case, if multiple, should suggest at once the probability of Recklinghausen's disease.

Fragilitas ossium (osteogenesis imperfecta) has normal serum calcium, phosphorus, and phosphatase; blue sclerae are often found in this condition. Paget's disease has a rather constant elevation of serum phosphatase with

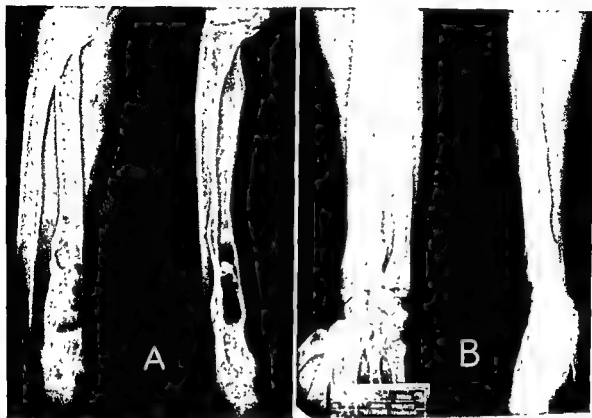


FIG. 354. Hyperparathyroidism. A, Residual cystic changes in radius following parathyroidectomy. B, Same case after curettage and bone transplantation. Note regeneration in the cystic areas.

normal calcium and phosphorus, and areas of bone affected are more sporadically located. The age incidence is between 40 and 60 years.

Solitary cyst occurs in young individuals and is usually noted before epiphyseal closure; chemical values are normal. The incidence of hyperparathyroidism in children is very low, there being less than 20 cases reported in the literature; of these, all but 3 were over 10 years of age.

Plasma cell myeloma occurs in older people and, save for a frequent elevation in serum protein, chemical levels are within normal limits. Bence-Jones bodies (albumosuria) in the urine are present in about 50 per cent of cases. Roentgenographic examination discloses a more punched-out appearance with intervening normal bone architecture.

In rickets and osteomalacia the serum calcium and phosphorus are usually depressed and the serum phosphatase elevated. The depression in serum calcium distinguishes these conditions from hyperparathyroidism. Moreover, in the former the bone is not absorbed but rather demineralized, whereas in hyperparathyroidism there may be true bone absorption.

Fibrous dysplasia is characterized by definitely circumscribed areas of

bone alteration while the remainder of the bone architecture is normal in appearance. The serum alkaline phosphatase may be somewhat elevated but there are no other chemical alterations in the blood.

It is important to suspect the possibility of hyperparathyroidism in any case in which there is diffuse malacic disturbance of bone, and the key to the correct diagnosis lies in checking this suspicion with appropriate chemical studies of the blood.

TREATMENT

An early diagnosis is based upon (1) the suspicion that this disease may be the cause of symptoms, following which (2) chemical studies of the serum calcium, phosphorus, and phosphatase and (3) complete roentgenographic examination of the skeleton are made. (4) The finding of a palpable nodule in the thyroid region is the final step. Once the diagnosis has been established, exploration of the parathyroids is indicated and removal of the adenomatous gland is usually followed by prompt relief of symptoms and recalcification of the bone areas involved. Where this treatment is carried out in advanced cases with cysts and giant cell tumors, complete return to normal may not be accomplished and surgical measures such as curettage and bone transplants may be necessary (see Figs. 353 and 354).

68. LESIONS OF BONE DUE TO METABOLIC DISORDERS

CERTAIN METABOLIC DISORDERS MAY GIVE RISE TO SIGNIFICANT CHANGES in the skeletal system; among these may be mentioned: gout, renal rickets, and a group of conditions due to disturbance in lipid storage.

Gout

It must be a rare occurrence when joint manifestations of gout give rise to symptoms, signs, and roentgenographic features which resemble those of bone neoplasm.

Gout is ordinarily a disease of rather insidious onset. Its course is more slowly progressive, and may be associated with long remissions of pain which is not true of bone sarcoma. Moreover gout is usually multiple in its manifestations.

Roentgenographic examination may disclose appearances which suggest a wide variety of bone and joint lesions. In some instances there is irregular periosteal new bone formation, and in others, bone erosion. These alterations are compatible with sarcomatous involvement. Other changes produced by gout may resemble an area of fibrous dysplasia or nonosteogenic fibroma (see Fig. 355). Large tophi in great toes may be mistaken for calcinosis or enchondromatosis. Bulky tophi about the knee may be suggestive of synovioma; smaller ones on the fingers may resemble xanthoma of tendon sheaths.

Other conditions which on rare occasions may have to be taken into consideration are Boeck's sarcoid, hyperparathyroidism, and Paget's disease.

For excellent roentgenograms of these lesions which may simulate gout the reader is referred to Talbott's article in the *Oxford Medicine*.

RENAL OSTEITIS FIBROSA (RENAL RICKETS)

Among the unusual forms of osseous fibrodystrophy one should include those which are associated with and due to chronic renal insufficiency. Such cases are known as renal osteitis fibrosa or renal rickets. The syndrome is more often seen in children where the term renal rickets is applicable.



FIG. 355. A, Gout involving the metatarso-phalangeal joints. B, Roentgenogram showing gouty involvement of metatarso-phalangeal joint. Note amorphous deposits of urates which somewhat resemble osteoid formation in a productive bone tumor. However, the bones are affected on either side of the joint which is very unusual in primary neoplasms of bone. The joint space is virtually obliterated.

However, it has been shown by Albright, Drake, and Sulkowitch that adults may be similarly affected and in such instances renal osteitis fibrosa is an appropriate term.

Fletcher and Parsons, in 1911, were the first to observe that renal insufficiency was occasionally the cause of rickets. Barber further described the condition in 1921, and Mitchell defined its etiology in 1930, at the same time offering an explanation of the pathologic physiology involved. His theory has been scientifically verified. In brief, it assumes that, owing to diminished excretion of urine, there is phosphate retention and that these retained phosphates are then excreted into the lumen of the bowel as a compensatory measure; here they combine with calcium which has already been ingested to form insoluble compounds, thus absorption of calcium in the diet is prevented. Such patients have a high serum phosphorus and a low serum calcium.

When seen in adults, this condition is generally, but not invariably, associated with a secondary (compensatory) hyperplasia of the parathyroids.

Diagnosis

Since the skeletal changes induced by this condition are indistinguishable from those seen in other forms of fibrocystic disease it is obvious that one cannot make a definite diagnosis on roentgenographic findings alone. However, if renal function is found to be seriously impaired in a patient with suggestive lytic lesions of bone and the serum calcium level is low while the serum phosphatase is elevated, one is justified in suspecting that renal osteitis fibrosa or renal rickets is present and the case should then receive the benefit of further laboratory investigation.

Treatment

Therapy is entirely predicated on attempts to relieve the underlying renal insufficiency. If it is due to some congenital or acquired defect in the urogenital tract, e.g., a ureteral stricture, then removing the obstruction will tend to restore normal blood-chemical constituents which may in turn favorably affect the osseous changes.

Seldom has this been attainable, however, for the kidney damage is generally irreparable.

Oral or parenteral administration of calcium is entirely ineffectual.

DISORDERS OF LIPID METABOLISM

There is a group of diseases of the reticulo-endothelial system associated with disturbances in lipid storage and with skeletal manifestations which make them of interest to those concerned with the differentiation of bone lesions. Of these the most important and clearly recognized are Gaucher's and Niemann-Pick's syndromes. While both are known to be due to

faulty lipid metabolism, they differ not only in their clinical and roentgenographic manifestations but in the particular lipid involved. Gaucher's disease involves cerebroside lipidosis (kerasin) while in Niemann-Pick's disease there is a phosphatid lipidosis. It has been asserted that Gaucher's and Niemann-Pick's diseases are true examples of lipid storage due to hyperlipemia in contrast to Hand-Schüller-Christian's disease which is primarily a granulomatous process; cholesterinization is secondary and occurs only with progression of the disease.

GAUCHER'S DISEASE

Gaucher's disease is a rare entity characterized by chronic anemia, splenomegaly, and large lipid-containing cells which are found in other parts of the hemopoietic system.

The most striking features of this form of lipid-storage disorder is its insidious onset, long course, and its periods of remission. It is often almost impossible to fix the exact time when the disease first appeared. Pain is usually the first complaint. It is described as deep-seated, dragging, intermittent, and usually referred to the femora. As fever often accompanies the pain it is readily ascribed to arthritis, neuritis, or osteomyelitis. Splenomegaly is the most constant and notable finding. It is advisable to palpate for splenic enlargement in all cases presenting the symptoms mentioned above. Bone and spleen constitute the notable foci of Gaucher's disease.

Clinical Course

This disease begins insidiously in infancy or childhood and has a predilection for females and the Jewish race.

In addition to bone pain and splenomegaly, enlargement of the liver, patchy skin pigmentation, and a tendency to bleed from the gums and to develop ecchymoses from trivial trauma are characteristics of the disease. There is a pronounced tendency to intermittent periods of exacerbation and remission with long intervals during which the patient may be symptomless and able to engage in normal activities. It is said that during the third and fourth decades physical efficiency diminishes and life is ordinarily terminated by some intercurrent disease, such as tuberculosis, yet cases have been known to live until late in their sixties.

The essential findings in this condition are the large cells in the spleen, lymph nodes, and bone marrow. They contain a lipid, kersin. The most abundant source of these cells is the spleen which may reach extremely large proportions.

Roentgenographic Appearance

The changes wrought in the skeleton by this disease are those of absorption, decalcification, sclerosis, and, accompanying these, destruction with deformities in the outline, especially of the femur and vertebrae.

Early in the disease an irregular demineralization of the femur and a peculiar alteration of the supracondylar region due to thinning of the cortex produces a characteristic "flasklike" appearance suggesting the outline of



FIG. 356. Bone changes due to Gaucher's disease. Note so-called "Erlenmeyer flask" appearance of lower femoral shaft.

an Erlenmeyer flask. These areas represent replacement of normal marrow by Gaucher cells (see Figs. 356-358).

Vertebral bodies constitute the most dangerous locations of bone alterations in this disease. Generally only one or two bodies are involved but outstanding destruction of many has been described. Here the appearance more closely resembles tuberculosis than neoplastic disease although disks and adjacent vertebrae are not involved.

Even with occasional collapse of a vertebral body paraplegia or other cord damage has not been reported.

Laboratory Tests

While the cells of Gaucher's and Niemann-Pick's diseases are quite similar, the former contain kerafin which gives a positive stain for iron but not for fat, whereas the latter contain a phosphatide which gives a negative test for iron but positive stain for lipid.

Treatment

Splenectomy is thus far the only therapeutic measure that has been of proved value. When it is successful there is an improvement in the symptoms and general condition and a slowing of the process of the disease, which nevertheless still persists in other parts of the reticulo-endothelial system.

NIEMANN-PICK'S DISEASE

This rare, familial, congenital disorder begins in infancy and in the majority of cases affects children of Jewish parentage. It is a disorder involving the cellular metabolism of histiocytes and reticular cells and can well be termed an essential lipid histiocytosis. The lipid involved is the diaminophosphatid, syringomyelin. In contrast to Gaucher's disease, where the lymphatic and hemopoietic systems are involved, the reticulocytes and histiocytes of all organs may be affected.

Clinical Features

The onset is insidious. Infants appear normal at birth, and for weeks and months their development is normal; then they begin to refuse food, steadily lose weight, and show retardation of growth. Abdominal enlargement is prominent and both spleen and liver increase to enormous proportions. Superficial lymph nodes may increase in size. The skin becomes dry and waxy with a brownish yellow pigmentation. Steady decline in both mental and physical condition progresses to early death.



FIG. 357. Gaucher's disease. Note slight fusiform expansion of upper portion of shaft of humerus.

Bone Changes

The skeletal changes are not nearly so noteworthy as those in Gaucher's and Hand-Schüller-Christian's diseases; this is no doubt due to the fact that



FIG. 358. Polycythemia vera. Note that roentgenographic appearance of lower femora is similar to that seen in Gaucher's disease.

the early infantile skeleton exhibits less definite evidences of the marrow alterations induced by the disease. Slight osteoporosis of the cranial bones and the major long bones are the only features, and patchy areas of decalcification have been observed by only one writer. Since the other aspects of this disease are so much more prominent, it should never be confused with other bone diseases and is, therefore, of only academic interest to us in a study of skeletal affections.

SCURVY

Because scurvy is associated with spontaneous hemorrhages it is sometimes the cause of subperiosteal hematoma in the shaft of the long bones which may give rise to tumefaction and produce roentgenographic features which may simulate osteogenic sarcoma (see Fig. 359). Such confusion has resulted in needless amputation of a limb. This, in spite of the fact that Chevallier, in his thesis on the roentgenographic aspects of scurvy, does not consider that bone sarcoma constitutes a difficult differential diagnostic problem.

Were it not for the widespread dietary deficiencies now prevalent in many countries as a result of postwar economic conditions, the rarity of infantile scurvy might make a discussion of its bone changes unnecessary in connection with neoplasms of bone.

Scurvy is seldom monostotic in its skeletal manifestations and if it is suspected a general roentgenographic survey of the bones is indicated. Osteogenic sarcoma on the other hand is monostotic. If occasional serious mistakes are to be avoided, radical treatment, either surgical or radiologic, should be postponed until histologic confirmation has been obtained.

70. CONDITIONS DUE TO ABSORPTION OF CHEMICAL POISONS

CERTAIN CHEMICALS, INCLUDING THE ELEMENTS FLUORINE AND PHOSPHORUS, have the property of inducing profound alterations in bone which are readily detectable on the X-ray films. Although it is unlikely that these changes would be mistaken for a neoplasm of bone, for the sake of completeness they are mentioned here.

FLUORINE

Fluoride deposits are notable in and around west Texas, particularly in Deaf Smith county in the Panhandle. The profession is now aware of the effect of the ingestion of soluble fluoride salts by the inhabitants of this section upon the development of dental caries, but the remarkable skeletal changes which are sometimes caused by such ingestion have not received much attention. The roentgenographic appearance is characteristic; it reveals a profound increase in the density of the bones; this is diffuse and affects all parts of the skeleton without any other apparent change. For example, the shape and texture of the bones are unaltered. There are no areas of destruction or of demineralization; in fact the picture is one of hypermineralization.

There are only two other conditions which produce comparable changes. Sclerosing osteogenic sarcoma can at times cause a similar increased density but it is, of course, limited to a portion of a single bone and the remainder of the skeleton presents a normal appearance. Osteopetrosis, on the other hand, has the same even, diffuse increase in density of the entire skeleton as is seen in fluoride cases but with an important distinguishing feature: the structure of the bone is lost in a homogeneous density which obliterates the bony trabeculae, and the transition from cortex to medulla is no longer clear-cut. Thus, if the films are viewed simultaneously one can readily identify osteopetrosis from fluoride poisoning, whereas if either condition is viewed alone it might readily be confused with the other.

Fluoride changes of marked degree were noted in a soldier from Big

Spring, Texas. The roentgenographic diagnosis at one Army hospital was that of Albers-Schönberg disease while at another it was thought to be fluoride poisoning. In order to settle the question a portion of rib was re-

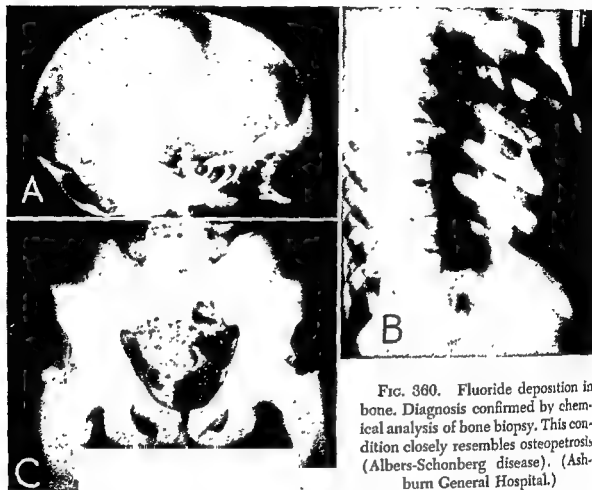


FIG. 360. Fluoride deposition in bone. Diagnosis confirmed by chemical analysis of bone biopsy. This condition closely resembles osteopetrosis (Albers-Schönberg disease). (Ashburn General Hospital.)

sected and its ash content of fluorine determined. The test established beyond equivocation the origin from fluorine (see Fig. 360).

Fluoride is present in normal bones which contain from 0.01 to 0.2 or possibly 0.3 gm. per 100 gm. of tissue. This patient's bone was reported by the Army Medical Center laboratory to contain 15 gm. per 100 gm.

Another case observed during the war involved a 22-year-old soldier who died in a general hospital of severe chronic nephritis and secondary anemia. The chalky teeth and characteristic roentgenograms of the bones pointed strongly to the diagnosis of chronic fluoride poisoning. This was confirmed by chemical analysis of the bones and teeth. This patient had resided in a part of Texas noted for the occurrences of this type of chronic poisoning from fluorine.

PHOSPHORUS

Ingestion of phosphorus may leave its mark in bone in the form of interference with bone growth. The striking "double exposure" effect is well shown in Figure 361.

LEAD

Sclerotic changes in bone due to lead poisoning have been recognized for some years. A recent report by Cooper describes such changes occur-



FIG. 361. Phosphorus poisoning, effect on skeletal growth of phosphorus ingested in early childhood.

ring as a result of the inhalation of fumes from burning automobile battery casings. In certain sections of the country during times of poverty, discarded battery casings are used for fuel. In a number of instances this practice has resulted in rather severe alteration in the bones of young children.

ROENTGENOGRAPHIC APPEARANCE

This condition causes increased density in the metaphyseal portions of the long bones, the anterior ends of the ribs, and in the iliac crests. It is homogeneous in character. If lead poisoning is suspected the diagnosis ought to offer no particular difficulty but if the films are made of only one bone, it is possible that the findings might be mistaken for osteoid osteoma, although, of course, no nidus would be apparent.

Treatment

This consists in the prevention of further exposure to the fumes of lead. With the passage of time these areas of density gradually tend to disappear.

71. CONDITIONS OF UNCERTAIN ETIOLOGY

PAGET'S DISEASE—OSTEITIS DEFORMANS

THIS CONSTITUTIONAL BONE DISEASE WHICH OCCURS IN MIDDLE-AGED OR elderly subjects was first described by Paget in 1877. It is marked by an insidious onset, chronic course, skeletal alterations, changes in serum phosphatase, tendency to pathologic fracture, and to complications by sarcomatous transformation. The bones most frequently involved are the skull, spine, pelvis, and sacrum; the ribs are rarely affected and the carpus, tarsus, and fibula practically never.

ETIOLOGY

Thus far the cause of this disease remains unknown. Paget suggested the name *osteitis deformans* because he regarded it to be an inflammatory process. This opinion was shared by others, including Looser, Albertini, Freund, Erdheim, and Haselhofer, who thought that the process was most likely due to prolonged chronic inflammation. Others have considered endocrine disturbances as a possible factor, stressing particularly parathyroid dysfunction. These patients, however, present no symptoms suggestive of hyperparathyroidism and thus far parathyroid adenomas have not been demonstrated in patients with Paget's disease nor have the serum calcium and serum phosphorus shown abnormal levels. Moehlig and Adler claim that the pituitary gland is the one primarily involved and that the parathyroid is affected secondarily. Dysfunction of the adrenals and the thyroid gland has also been considered as having an etiologic connection but thus far convincing proof on this point is lacking. Likewise other factors suggested, i.e., arteriosclerosis, trauma, heredity, and syphilis have very little supportive evidence.

Reifenstein and Albright have advanced an ingenious explanation of the factors responsible for the appearance of bone lesions in Paget's disease. They maintain that this is a localized rather than a generalized bone affection because, while the process is a spotty one, there are entirely normal areas in which there is no apparent sign of the disease. For this reason they argue it is not a metabolic or endocrine disorder. They make a com-

parison of the lesions in Paget's disease and Recklinghausen's disease of bone. The lesions in both are extremely vascular, show marked fibrosis and, in both, about half of the bone surface is covered with osteoclasts and about half with osteoblasts—evidence that there are marked bone resorption and bone repair. The two conditions show the following differences: In Recklinghausen's disease there is a tendency to osteoclastomas or "brown tumors." The bone architecture is different since in Recklinghausen's there is a good mechanical arrangement of the trabeculae while in Paget's disease the trabeculae start anywhere and end anywhere; moreover in the latter disease the characteristic mosaic structure is striking and is felt to be due to a bizarre arrangement of the cement lines within the trabeculae. Schmorl and Albright have independently shown that in Paget's disease bone destruction appears to precede bone production and is the initial lesion. A comparison of the two conditions is shown in Table XLVIII.

TABLE XLVIII

DIFFERENTIAL DIAGNOSIS BETWEEN RECKLINGHAUSEN'S AND PAGET'S DISEASES

	RECKLINGHAUSEN'S DISEASE	PAGET'S DISEASE
ETIOLOGY	Parathyroid adenoma	Unknown
EXTENSION	Generalized throughout skeleton	Always many normal bones
HISTOLOGY	Hyperactivity of osteoclasts	Mosaic structures
GIANT CELL TUMORS	Often present	Never present
ROENTGEN PICTURE	Generalized decalcification of cortex with dilatation of Haversian canals	Thickening of cortex with a new, mainly fibrillar, architecture; often periosteal bone formation
AGE	Young and old	Above 40 years
BIOCHEMICAL SYNDROME	Increased serum calcium, decreased serum inorganic phosphorus, increased phosphatase, increased calcium and phosphorus in urine	Calcium and phosphorus in serum and in urine normal. increased serum phosphatase

Reifenstein and Albright interpret the pathologic physiology of Paget's disease as follows: Bone destruction occurs from some hitherto undiscovered cause. This renders the bones more susceptible to stresses and strains, which in turn stimulate osteoblasts to lay down more matrix with a resultant rise in the phosphatase level. In the long bones and vertebrae bone repair occurs almost simultaneously with bone destruction.

When a patient with Paget's disease is immobilized there exists the danger of "chemical death" because of the resulting high blood calcium level giving rise to anuria. Therefore in these cases the period of immobilization should be as early and as brief as possible and accompanied by a low calcium and high fluid intake.

SYMPTOMS AND CLINICAL FINDINGS

The first symptom noted by the patient may be an increase in the size of his head (see Figs. 362-363) or a progressive bowing of the long bones of his

lower extremity (see Fig. 363). Pain is inconstant and seldom severe. It is characteristic of the disease that it may persist for many years without causing any alteration in the patient's general health or any inconvenience other than



FIG. 362. Paget's disease. In this case the marked involvement of the facial bones gave an appearance resembling leontiasis.

that due to the changes in the size, shape, structure, and contour of the bones. It is probable that prolonged weight-bearing acts on softened bone to cause deformities such as anterior bowing of the lower extremities (see Fig. 364). Pathologic fracture of the long bones is not common. When it occurs it is nearly always transverse. Deafness is frequent and is of the otosclerotic type attributable to involvement of the petrous portion of the temporal bone.

The disease is more frequently seen in its polyostotic form yet there are cases on record where but one bone appears to be involved. It would be necessary to have definite evidence that this mono-

stotic form persisted over a long period of time before accepting the actual existence of this type.

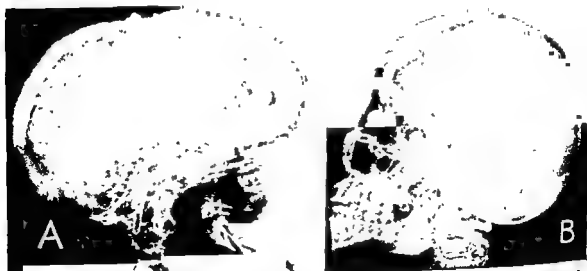


FIG. 363. A, Paget's disease showing skull involvement. B, Hyperostosis frontalis interna.

DIAGNOSIS

If the condition is suspected and roentgenographic examination is carried out the diagnosis is not difficult because the bone changes thus revealed are quite characteristic. Changes in shape, size, and structure of bone occur.

The author has long been of the opinion that the sarcoma seen in bone already affected by Paget's disease differs from the ordinary osteogenic sarcoma. Codman shared this view and suggested the term *Paget's sarcoma*.

Probably a better term would be *sarcoma complicating Paget's disease*. These tumors lack the histologic appearance of true bone-forming sarcomas and resemble fibrosarcoma. Although some show no osteogenic features and are truly spindle cell or even polymorphocellular, others do show a definite tendency to deposit intercellular matrix and bone. Giant cells are a frequent finding and some cases present the picture of malignant giant cell sarcoma. In the latter, unless one had cognizance of the existence of Paget's disease, a diagnosis of malignant giant cell tumor would probably be made on the histology alone.

It is apparent, therefore, that whatever the true nature of this sarcoma it does not conform to a single pattern and differs from ordinary osteogenic sarcoma in its more frequent tendency to develop in several bones either concurrently or, more often, consecutively. To avoid confusion, however, the term *osteogenic sarcoma* is used in this chapter, though reluctantly, to designate the type of malignant tumor seen in patients with Paget's disease.

Delafield maintained that the incidence of sarcoma among patients with Paget's disease was no greater than in any group of similar age. This is contrary to the opinion of the majority of observers and it now seems to be firmly established that, at least as regards the occurrence of osteogenic sarcoma, Paget's disease is a predisposing factor.

Packard, Steel, and Kirkbride reviewed the literature up to 1901 and collected 66 cases of undoubted osteitis deformans in which there was an associated sarcoma in 5, or 7.5 per cent. DaCosta, in 1915, assembled 213 cases in which sarcomatous disease of some form developed in 9.5 per cent. Gruner, Scrimger, and Foster reported that in about 9 per cent of their cases of Paget's disease this condition was associated with sarcoma.

Bird studied the records of four large Boston hospitals with some interesting results. He was able to collect 64 cases of osteitis deformans, in 7 of which (approximately 11 per cent) sarcoma occurred. He estimated that there is 1 case of Paget's disease in every 15,000 admissions to hospitals in Boston. This corresponds closely with the record of 1 in 10,000 at Johns Hopkins Hospital, 1 in 13,000 at Jefferson Hospital, and 1 in 16,000 at the Mayo Clinic. At Peter Bent Brigham Hospital there were 15 cases of osteitis deformans in 45,000 admissions, or 1 in 3,000. Bird explained the latter figures on the theory that a far greater percentage of patients in that hospital had had roentgenograms taken (89 per cent). The disease is probably not so rare as the statistics of the various hospitals would suggest. In the first place, many patients do not enter hospitals unless some complication arises and even then they may be classified on the records of the hospital according to the complication and not indexed as Paget's disease.

Moreover, as Bird pointed out, early examples of the disease are being constantly overlooked especially when it is confined to a single bone.

In 1931, Sharp and the author studied a total of 71 cases of osteogenic sarcoma in patients over 50 years of age. Twenty were collected from the records of Memorial Hospital and 51 were from the Bone Sarcoma Registry. As shown in Table XLIX, the association of sarcoma and Paget's

TABLE XLIX
ASSOCIATION OF OSTEOGENIC SARCOMA AND PAGET'S DISEASE*

	MEMORIAL HOSPITAL SERIES	BONE SARCOMA REGISTRY SERIES	TOTAL
Number of patients over 50 years of age with osteogenic sarcoma	20	51	71
Number of patients over 50 years of age with osteogenic sarcoma and Paget's disease	6	14	20
Percentage of cases with two diseases associated	30	27.4	28

* Case E. S. in the series from Memorial Hospital is also included with the Bone Sarcoma Registry series

disease is relatively the same in the two series, i.e., Memorial Hospital series, 30 per cent; Bone Sarcoma Registry series, 27.4 per cent, with an average percentage of 28 for the total number. Such a frequent association of two apparently dissimilar diseases justifies a careful study of the features presented in the various cases.

A group of all patients over 50 years of age with osteogenic sarcoma was studied. As shown in Table L, the incidence of osteogenic sarcoma de-

TABLE L
DECREASE OF FREQUENCY IN INCIDENCE OF OSTEOGENIC SARCOMA IN PATIENTS OVER FIFTY YEARS OF AGE*

AGES BY HALF DECADES	PATIENTS WITH OSTEOGENIC SARCOMA ALONE	PATIENTS WITH OSTEOGENIC SARCOMA AND PAGET'S DISEASE
50 to 55	18	1
55 to 60	13	6
60 to 65	8	5
65 to 70	7	6
70 to 75	5	2
75 years and over	1	0

*Coley, H. L., and Sharp, G. *Arch Surg.* 23: 918, 1931

creases in each half-decade age group over 50 years. The oldest patient with osteogenic sarcoma recorded in the Bone Sarcoma Registry was 77 years of age; in this case the sarcoma was not associated with Paget's disease. In the Memorial Hospital series there were no cases of Paget's disease complicated by osteogenic sarcoma in patients under 50 years of age. There were, however, 4 cases in the Bone Sarcoma Registry of osteogenic sarcoma associated with Paget's disease in patients under the age of 50. Three of the patients were men and 1 was a woman. Their ages were 35, 37, 42, and 47, respectively. In the half-decade age groups, the highest percentage

was found in persons between 65 and 70 years of age, in which 6 of the 7, or 85.7 per cent, of the patients with osteogenic sarcoma had Paget's disease. The percentages decrease above and below this peak.



FIG. 365 Osteogenic sarcoma of the skull developing on the basis of Paget's disease.

The sites of predilection of osteogenic sarcoma in the skeleton in patients over 50 years of age correspond closely to those found at any age except for the increase in frequency of involvement of the flat bones, as shown in Table LI. Involvement of the scapula is particularly common, appearing in 9 of the 51 cases, although none of these was associated with Paget's disease. Approximately 60 per cent of the osteogenic sarcomas of the tibia, humerus, and ilium, and 100 per cent of the cases of osteogenic sarcoma of the skull occurred on the basis of a preexisting Paget's disease (see Fig. 365). In a patient over 50 years of age presenting an osteogenic sarcoma of the skull there is a strong probability of an associated Paget's disease.

When Paget's disease was present, it was demonstrated by roentgenographic examination in the bone involved by the osteogenic sarcoma; in no

TABLE LI
LOCATION OF PRIMARY TUMORS
OSTEOGENIC SARCOMA AND PAGET'S DISEASE

LOCATION	OSTEOGENIC SARCOMA IN ALL PATIENTS OVER 50 YEARS OF AGE	OSTEOGENIC SARCOMA AND PAGET'S DISEASE IN SAME AGE GROUP
<i>Long bones</i>		
Femur	28	6
Humerus	8	5
Tibia	6	4
Ulna	2	0
Mandible	1	0
Radius	1	0
Clavicle	1	0
Fibula	1	0
Rib	1	0
Metacarpal	1	0
<i>Flat bones</i>		
Vertebra	1	0
Scapula	9	0
Ilium	5	3
Skull	2	2
Ischium	2	1

instance was the sarcoma found to affect a portion of the skeleton free from roentgenographic evidence of Paget's disease (see Figs. 366-368).

The duration of Paget's disease prior to the appearance of osteogenic sarcoma is difficult to determine either by history or by the physical examination. The patient may have had this disease many years before attention was attracted to the insidious changes taking place. This is particularly true in women. However, the disease is rarely reported in patients under 30 years of age and seldom in patients under 40 or 45 years—an important observation as osteogenic sarcoma is rarely found to complicate it until the age-group of 55 to 60 is reached. It seems highly probable that an interval of from ten to fifteen years is present between the onset of Paget's disease and the appearance of a complicating osteogenic sarcoma. In the histories we find this partially substantiated. Only 5 of the patients were aware of Paget's disease with its deformities. Two of these gave a positive history of a duration of eight years; 1, "many years," 1, ten years, and the fifth, twenty years. One of these patients with Paget's disease was under our observation for ten years and developed an osteogenic sarcoma at the distal end of the humerus. The question may be raised of the possibility of two or more osteogenic tumors arising on the basis of Paget's disease in one patient. This was demonstrated in 2 patients in the Memorial Hospital series. These are believed to be examples of multiple primary sarcomas as, ordinarily, osteogenic sarcoma infrequently metastasizes to bone.

Paget's disease causes an elevation in the serum alkaline phosphatase which may reach levels ranging from 15 to over 100 Bodansky units. The only other two conditions of bone known to affect such a pronounced ele-

vation are osteogenic sarcoma and prostatic cancer metastatic to bone. Since the phosphatase is elevated in both Paget's disease and osteogenic sarcoma, it would be anticipated that there would be an increase in phos-



FIG. 366



FIG. 367

FIG. 366. Sarcoma of femur complicating Paget's disease. Note the bowing of the opposite tibia.

FIG. 367. Osteogenic sarcoma of upper humerus arising on basis of Paget's disease. Treatment: interscapulothoracic disarticulation. Patient developed a secondary sarcoma of the upper femur and eventually died of the disease.

phatase in the serum when the two conditions exist simultaneously. This proves to be the case. (For further details see Chap. 5, p. 66.)

TREATMENT OF PAGET'S DISEASE

No form of therapy has resulted either in a cure or even in substantial alteration of the natural course of osteitis deformans. Roentgen therapy has been used for relief of bone pain and is sometimes successful. It is important to keep patients under observation indefinitely in order to detect a complicating bone sarcoma as early as possible.

TREATMENT OF SARCOMA DEVELOPING ON PAGET'S DISEASE

Patients with Paget's sarcoma have had a uniformly fatal outlook. We are not aware of a single reported five-year survival. Radiation has been tried

in the majority of cases seen at Memorial Hospital. Amputation was performed in 12 of the 14 cases in the Bone Sarcoma Registry series. Despite the ultimately hopeless outlook, amputation seems to be the method of

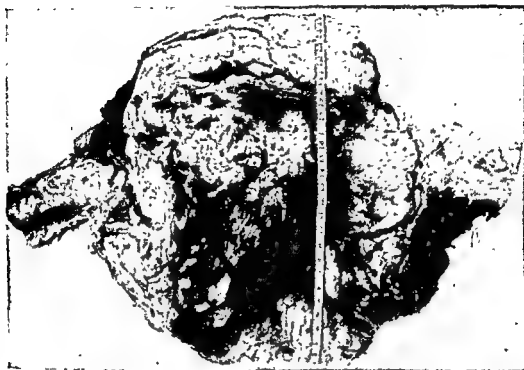


FIG. 368. Gross specimen of osteogenic sarcoma of femur developing on Paget's disease (see Fig. 366, p. 668).

choice in view of the painful character of the growth. Successful efforts to arrive at an earlier diagnosis may conceivably bring about a less gloomy prognosis. However, we may expect that success will have to wait on a better understanding of the relation of Paget's disease to sarcoma and a knowledge of its cause and prevention.

The 100 per cent mortality rate of patients suffering from osteogenic sarcoma associated with Paget's disease may be explained on several counts. In the first place, patients who are accustomed to the "growing pains" associated with Paget's disease are not apt to seek medical advice for a change in the character of the pain as promptly as would patients with osteogenic sarcoma unassociated with Paget's disease. In the second place, the pathologic changes due to Paget's disease may delay the onset of pain from an osteogenic sarcoma. Finally, osteogenic sarcoma arising in Paget's disease may have more malignant qualities than has this primary tumor of bone in normal patients past middle life. This may in part account for the fact shown in Table LII that a patient with osteogenic sarcoma alone lives about ten months longer than does the victim of sarcoma developing on a pre-existing Paget's disease.

Osteitis deformans is a condition that should engage the interest of those

TABLE LII
DURATION OF LIFE
OSTEOGENIC SARCOMA AND PAGET'S DISEASE

SERIES	NUMBER OF CASES	PATIENTS OVER 50 YEARS WITH OSTEOGENIC SARCOMA (AVERAGE NUMBER OF MONTHS)	NUMBER OF CASES	PATIENTS OVER 50 YEARS WITH OSTEOGENIC SARCOMA AND PAGET'S DISEASE (AVERAGE NUMBER OF MONTHS)
Memorial Hospital	10	18.7	4	16.0
Bone Registry	23	26.3	11	14.4
	33	24.0	15	14.8

concerned with bone neoplasms for it may be, as Codman suggested, that a fuller understanding of this condition might provide us with the key to the etiology of some forms of bone sarcoma.

It is important to keep all patients with osteitis deformans under continuous careful observation and to have roentgenograms made at regular intervals over an indefinite period so that we may detect sarcomatous degeneration promptly and thus, perhaps, improve the present almost totally hopeless outlook.

OSTEOPOROSIS CIRCUMSCRIPTA

The term *circumscribed osteoporosis* was introduced by Schüller in 1926. Moore, in an article on Paget's disease published three years previously, had described similar changes in one of his cases. Sosman (1927) was the first to suggest that osteoporosis circumscripta might be the "absorptive or destructive phase of Paget's disease with the productive phase held in abeyance." In 1932, Kasabach and Dyke reported 15 new cases 8 of which they stated showed sclerotic changes typical of Paget's disease either in the skull or elsewhere and which they were inclined to regard as a precursor of Paget's disease.

Simonetta's contribution to the subject in 1937 covered 47 cases; in 32, the osteoporosis circumscripta of the skull was associated with typical Paget's disease somewhere in the skeleton. The high serum phosphatase level—essentially normal in osteoporosis circumscripta but characteristically elevated in Paget's disease—was also present.

Since the report of Simonetta a careful search of the literature up to and including 1945 has failed to disclose any other reports of cases of osteoporosis circumscripta.

In support of the theory that it is related to or a manifestation of Paget's disease more than two-thirds of the reported cases showed other skeletal manifestations of the latter. Moreover in cases where the skull films revealed osteoporosis circumscripta and skeleton films were negative for Paget's disease, follow-up studies disclosed that in from two to eight years Paget's disease developed in or adjacent to the areas of osteoporosis.

Our interest in this condition is largely one of diagnosis and it should be thought of in connection with sharply circumscribed areas of radiolucency in adults from 30 to 60 (see Fig. 369). Such cases should be followed in-



FIG. 369. Osteoporosis circumscripta. Probably an early phase of Paget's disease of the skull.

definitely since they will probably emerge as full-blown cases of Paget's disease and subject to the complications that are common to it.

LEONTIASIS OSSEA

The term "leontiasis ossea" was coined by Virchow in 1865 to designate proliferative changes in one or more of the facial bones. The proliferative process is always hyperostotic and may encroach on foramina or fossae and press upon cranial nerves. The condition often commences in the superior maxilla and may affect any of the other bones of the face and jaw, less frequently the calvarium. By intrusion upon the structure adjacent to the affected bone or bones, it may cause pressure symptoms such as headache, nasal obstruction, and suppurative dacryocystitis; speech and mastication may be interfered with. Amblyopia exophthalmus and blindness may result from narrowing of the optic foramina. Cerebral symptoms such as psychic manifestations and convulsions have been described.

DISTRIBUTION

Age. The condition develops as a rule in young individuals either at, or shortly after, puberty. In 80 per cent the onset is prior to the age of 20.

Sex. Sex seems to play no part in the disease. Males are more often affected than females, though the disparity is not marked.

In 35 cases collected by Reisz the distribution of the affected bones was as follows:

Maxilla	19
Zygoma	14
Frontal bone	13
Parietal bone	13
Mandible	12
Nasal bones	11
Alveolar process of maxilla (isolated)	6
Temporal bone	6
Occipital bone	4
Bones of orbit	4
Sella turcica	4
Palate	3
Base of skull	3
Sphenoid	2

ETIOLOGY

Since leontiasis ossea is a descriptive term, or syndrome, it should be understood at the outset that it is not a pathologic entity and probably there are a number of different types which have different etiologic factors.

Localized Paget's disease, chronic or creeping periostitis, diffuse osteitis, changes due to fibrous dysplasia, cystic lesions of hyperparathyroidism, and finally true neoplasms of slow growth are all possible factors in the production of the changes known as leontiasis ossea.

Knaggs has stressed the numerical importance of the periostitic and osteitic form of the disease. Hamburger and Nachlas in 1926 described the condition as a manifestation of Paget's disease, as did Abbe eighteen years earlier. Ivimey was the first (1929) to report a case of bone dystrophy associated with leontiasis ossea, which seems to have been an example of polyostotic fibrous dysplasia confined to the long bones of the right side of the body and all the bones of the skull. The influence of trauma is suggested in Gill's case and remarked upon by Boit and Sheehan.

CLINICAL FEATURES

The history of these cases is usually a prolonged one and relates to the discovery of the facial abnormality. Deformity may appear so gradually as to escape the patient's notice, but it is usually obvious to others. Tinnitus and other head noises, headache, optic neuritis, nasal obstruction, speech defect, and exophthalmus are other complaints.

The term, *leontiasis*, is one of great antiquity and was originally applied to cases of leprosy with rough and seamed thickening about the face, which suggested the muzzle of a lion. The appearance of the cases of leontiasis

ossea is rather characteristic. The deformity consists of prominent protrusions of the face and skull which may be asymmetrical.

ROENTGENOGRAPHIC APPEARANCE

Since this syndrome, as has been stated, is a topographic one and may be caused by a number of obscure disease conditions, one would expect marked variation in the roentgenographic appearance. Briefly stated the bone changes are osteoblastic, osteoclastic, or a combination of both. The texture of the bone has suggested a number of descriptive terms, e.g., "cottonlike rarefaction," "fluffy," "moth-eaten," "woolen-cloth."

TREATMENT

Unfortunately no form of therapy has proven to be of much avail. Surgical interference in an attempt to restore a more normal facial contour has not been particularly successful and roentgen therapy has likewise been of little use.

PROGNOSIS

The extremely slow progress of the condition is a constant feature. It can only be said to endanger life indirectly by causing pressure on neighboring structures. Only as we learn more about the treatment of the obscure underlying diseases which cause it can the outlook for sufferers from leontiasis ossea be improved.

OSTEOPETROSIS

This rare generalized bone affection was first described by Albers-Schönberg 40 years ago; he called it *marble bones* (marmorknochen). It is fundamentally characterized by increased density of both the cortical and cancellous bone of the entire skeleton. In 1941 Higinbotham and Alexander found only 131 cases reported in literature. Bone biopsies and autopsies in a score or more of cases have established the fact that the lamellae are increased and densely packed in cortical bone and the number and thickness of the trabeculae are increased in cancellous bone. These changes may result in such profound alteration that the gross distinction between these two portions of bone is lost. The marrow is definitely encroached upon and hemopoietic activity may be diminished. Apparently there is no definite evidence of an alteration in the chemical composition of the bone.

Symptoms are surprisingly lacking although pathologic fractures are often observed. There is an anemia of secondary type which may be due to inhibition of the hemopoietic activity or to mechanical crowding of the marrow cells concerned with blood-cell formation. Autopsy has shown this anemia to be proportional to the encroachment on the marrow space. In

such cases, the spleen, liver, and lymph nodes have been found to be active in taking over part of the function of the marrow.

In children, hydrocephalus, optic atrophy, and deafness may be caused

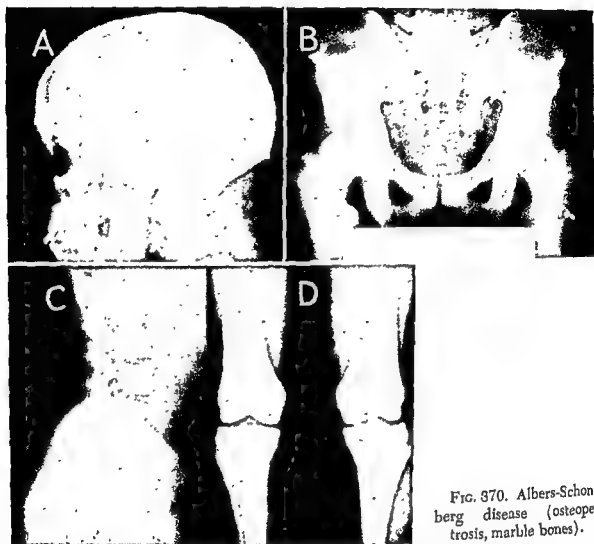


FIG. 370. Albers-Schönberg disease (osteopetrosis, marble bones).

by the obstruction of venous return flow from the cranial cavity as a result of narrowing of the foramina through which cranial nerves emerge.

An associated syndactylism and dyschondroplasia are suggestive of an hereditary basis for the disease. Certainly familial traits are striking; for example, Higinbotham and Alexander reported 4 siblings with obvious evidence of osteopetrosis and it may be inferred that they inherited the tendency to the disease from their mother. Consanguinity of parents has been a frequent occurrence, noted in about half of the reported cases. It has been considered that the condition is a recessive Mendelian character. Sex, age, and race seem to play no part. Blood-chemistry studies reveal no alterations that can be considered characteristic or even suggestive. The etiology is still unknown. Vitamin deficiency, endocrine disturbance, and other theories have no basis, and our present knowledge is limited to the view that it is a faulty differentiation of bone from mesoblastic tissue or, in other words, an anomaly of osteogenesis.

ROENTGENOGRAPHIC APPEARANCE:

Films of the skeleton show such a marked increase in density as to suggest that they have been greatly underexposed. This mistaken impression



FIG 371. Albers-Schonberg disease (marble bones or osteopetrosis). *Top*, note massive facial structures, extreme prognathism, and poor occlusion of teeth, *bottom*, roentgenogram of face showing extreme opacity and blurring of outline of bones.

may result in some cases being overlooked entirely. All the bones show this increased density which causes a partial or complete loss of the normal architecture of the bone (see Figs. 370 and 371). Prognathism has been observed and was present in the 4 cases reported by Higin-

botham and Alexander. Transverse bands of altered bone density may be seen in the shafts of bones lying parallel to the position of the epiphyseal line.



FIG. 371 (*Continued.*) Note characteristic increased density of bones of hand and wrist with peculiar barrel-shaped metacarpals and phalanges. (Courtesy of J. C. Lifton, D.D.S., *Am. J. Orthodontics* 33:325, 1947.)

DIAGNOSIS

After complete skeletal films have been obtained, the only condition with which this lesion can be readily confused is that caused by retention of fluoride salts due to chronic fluoride poisoning. This may give an appearance so similar as to make it extremely difficult to decide which of the two is responsible for the roentgenographic findings. This form of chronic intoxication with osteosclerosis has been described as occurring among workers in a Danish cryolite factory. Films of a case that came to autopsy at El Paso, Texas, were recently seen; here chemical studies on bone established the diagnosis. Another case was seen in a young soldier who had spent his life in West Texas (see p. 658). In the Panhandle of Texas there is a county where the water supply contains fluorine in sufficient concentration to cause discoloration of the teeth of the residents, and the dental profession has observed that these people are strangely immune to tooth decay. It is believed, therefore, that in some sections of this country cases

may occur in which this differential diagnostic problem might be encountered.

The following points are helpful in distinguishing between osteopetrosis and fluoride poisoning: In osteopetrosis the bone architecture is almost obliterated while in fluoride poisoning it is preserved. In fluoride poisoning the epiphyses are affected so that they remain roentgenographically demonstrable long after the age at which they ordinarily disappear. In osteopetrosis the bone is more dense and hard, and is resistant to the chisel at biopsy. It is therefore incorrect to assume that the finding of hard bone at operation in a case of supposed osteopetrosis is strong evidence that the condition is in reality one of fluoride poisoning.

COMPLICATIONS

An unique case presented by Kerr in 1936 is concerned with the development of a typical sclerosing osteogenic sarcoma of the femur in a Negro male of 20, who also presented the roentgenographic picture of osteopetrosis. He died with pulmonary metastasis. This case is notable as being the only one of osteopetrosis reported in a Negro and also because it is the first case observed in which osteopetrosis and osteogenic sarcoma were associated. Whereas osteopetrosis is not accompanied by an elevated serum phosphatase, it is interesting to note that this patient, due unquestionably to the presence of the tumor, had a serum phosphatase of 32.8 units which is in accordance with expectations in uncomplicated cases of osteogenic sarcoma.

TREATMENT

Thus far no treatment for osteopetrosis has been suggested that affects the patient's course favorably. It is not likely that being a diffuse process of an hereditary nature much can be done to relieve it.

OSTEOGENESIS IMPERFECTA (OSTEOPSATHYROSIS, IDIOPATHIC BONE FRAGILITY, BRITTLE BONES)

Hereditary or developmental fragility of bone, to which is attached such a multiplicity of names as to confuse the student—Vrolik in 1849 first termed it osteogenesis imperfecta—is a generalized disorder related to no known metabolic disturbance or disease. It is characterized by a failure of osteoblasts to lay down cortical bone and of endosteal cells to lay down bone in the spongiosa. There is a tendency to spontaneous fracture which may occur after trivial trauma.

One should exclude from this group instances of osteomalacia, osteopetrosis, and other bone abnormalities which present a clear clinical picture. Its hereditary and congenital features have long been recognized and

recent writers affirm them. Key considers heredity a factor of fundamental importance, claiming that the tendency is transmitted as a dominant character; thus if one parent is affected, half of the offspring will have the condition. In contrast to hemophilia, a generation is not skipped. This means that though born of affected parents, children who have normal bones and sclera will have normal children. Only about a third of the cases have an hereditary taint; the nonhereditary type, however, do not differ either clinically or roentgenographically enough to be distinguishable. Those with the nonhereditary congenital type so seldom marry and have children that there is small likelihood of this form being transmitted. Bickel, Ghormley, and Camp have offered the following classification:

A. Hereditary type

1. Blue sclera—characteristic roentgenographic changes
2. White sclera—characteristic roentgenographic changes
3. Blue sclera—atypical roentgenographic changes

B. Nonhereditary congenital type

1. Blue sclera—characteristic roentgenographic changes
2. White sclera—characteristic roentgenographic changes

It is also possible to classify cases on the basis of age at the time the disease is recognized, i.e., (1) fetal cases, (2) infantile cases, (3) adolescent cases, and (4) late cases.

CLINICAL FEATURES

Age is of importance since the hereditary type is not recognized until the age of 30 years as compared with 15 for the nonhereditary congenital type. Sexes are equally affected.

There is a great variation in the intensity of the disease which is usually in inverse ratio to the patient's age at onset. Thus, in the newborn it is sometimes fatal while in the adult it may be recognized only incidentally to an examination for some other, and totally unrelated, condition.

Deformities resulting from fractures of the axial skeleton or the long bones are the most striking objective findings. Stature may be short due to loss of bone length resulting from many fractures with healing in a position of malalignment. Skull deformity, failure of closure of sutures, poor dentition with soft, carious teeth are noticeable features.

Fractures are usually "greenstick" or subperiosteal and seldom produce over-riding. Angulation is common and may produce marked deformity. Fractures have been described involving every bone in the body. Pseudo-fractures, incomplete fractures, or regions of absorption, are not uncommon. In suspected cases these should be looked for on skeletal films. Fractures of the long bones predominate and the lower extremities are more often involved. There is usually a definite, although slight, initiating trauma and these fractures should perhaps not be termed *spontaneous*. Blue sclerae

are practically never absent in the hereditary type and are found in about 75 per cent of the cases with the nonhereditary congenital type. Otosclerosis, with early development of deafness, is not uncommon; it is found more



FIG. 372. Osteogenesis imperfecta (fragilitas ossium).

often in the hereditary cases than in those with the congenital (nonhereditary) form.

ROENTGENOGRAPHIC APPEARANCE

Brailsford has shown that roentgenographic study has greatly aided the classification of this disease, the determination of its degree, and the nature of the bone changes (see Fig. 372). He states:

Further contribution to the confusion has been due to the lack of uniformity in interpreting the histologic appearances. Consequently we must look elsewhere for evidence which will permit us to decide the degree, phase and nature of the bone changes in individual cases and to classify them. Radiography affords this evidence. It permits us to study the whole skeleton at any one time and by periodical examination to watch its development throughout the years and any complications which may occur. From the radiographic evidence it is possible to gain a very good indication of the nature of the tissue changes and anticipate the histological structure in different sites, i.e., in the foetal form the radiographs show a skeleton, the elements of which have a thin shell of bone for a cortex, the internal structure showing a granular appearance indicating calcification rather than ossification; the infantile examples in some cases show in the diaphyseal and epiphyseal regions of the metaphysis multiple rounded bony cell-

like structures up to $\frac{1}{4}$ inch in diameter enclosing non-osseous tissue, the appearance is similar to the lobulated cartilaginous structures we see in enchondroses. The adolescent and adult examples show slender shafts composed of a coarse cancellous tissue. Though many cases show similar progressive clinical developments the radiographs indicate very material differences in the behavior of the bone in others.

In some the changes are similar throughout the skeleton, usually more marked in the lower extremities, but in others you may see a very thin skull associated with changes in the bones of the hands and feet, some degree of general osteoporosis, bending and flattening of the ribs but little else.

Long bones show thinning and porosity of the cortex with a correspondingly enlarged medullary cavity. Porotic changes are more pronounced in the lower than in the upper extremity. Epiphyses are seldom altered; when they are, it is due to the distortion caused by trauma or weight-bearing. Closure of the epiphyses occurs at the normal age. In cases seen with their first fracture a helpful corroborative finding is mosaic rarefaction in the skull.

PATHOLOGY

The most marked deformities are found in the long bones. They are slender, the cortex is thin, and trabeculae are absent or else occur only in a fragmentary form. The periosteum is thin and inactive while marrow spaces are enlarged. Fractures are often subperiosteal without displacement and callus after fracture occurs promptly.

The shafts of the bones on section are soft. The epiphyses may be relatively normal until late in the disease when degenerative changes may appear.

Microscopic sections reveal a complete loss of the normal structure of bone with the haversian canals appearing as wide spaces interspersed with embryonal osteoid tissue. Bone lamellae are lacking. Fibroblasts, chondroblasts, and transitional cells replace osteoblasts. Sections taken through an area of callus formation may reveal cartilaginous tissue with extensive areas of necrosis.

In the diaphyseal portion of the bone necrotic areas are seen. The histologic changes in the more severe congenital forms of this disease bear some resemblance to those found in infantile scurvy. The blood findings are not distinctive.

TREATMENT

There is no known form of therapy that can be considered specific. This is to be anticipated in view of the apparent etiology in a defect of the germ plasm. Endocrine therapy has not been successful in the hands of most

investigators, although Hansen has tried extracts of the thymus. Vitamin-enriched diet, calcium salts, and cod liver oil may be prescribed.

Immobilization of fracture is indicated. When deformities occur, they

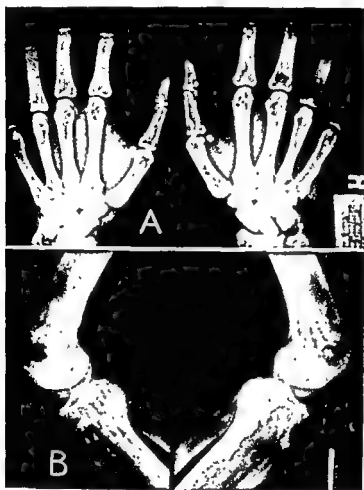


FIG. 373. Osteopoikilosis, "spotted bones." If skeletal films are not taken the presence of these areas in a long bone might be interpreted as metastasis of osteoblastic type, i.e., prostate.

may require correction. Nonunion does not yield very successfully to open operative measures. Fortunately, it is seldom encountered.

OSTEOPOIKILOSIS (SPOTTED BONES)

This term is used to describe a rare entity consisting of areas of increased density, small, ovoid, and slightly elongated, scattered throughout the spongiosa of the epiphyses and metaphyses of long and flat bones. While any portion of the skeleton may be affected the extremities are predominantly so, the skull, ribs, and spine are rarely involved.

Since this condition gives rise to no symptoms, its discovery is always accidental. Patients are usually in excellent health and the disease is disclosed as a result of incidental roentgenographic examination. No definite concept of its etiology has been offered. It may be familial or hereditary.

Thus far only about 50 cases have been reported; several others were recently discovered among soldiers in the Army hospitals who were radiographed for traumatic conditions.

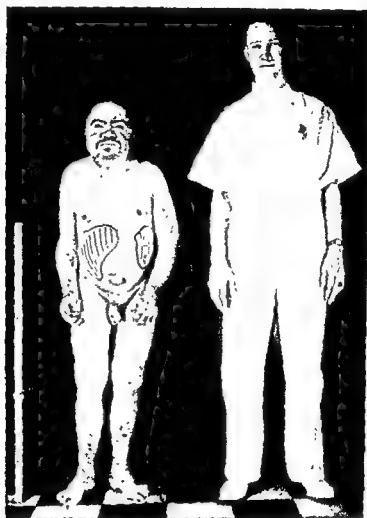


FIG. 374. Hurler's syndrome (gargoylism).

Holly found that the characteristic ovoid, dense areas are not constant either in size or visibility. In children they may enlarge or disappear and new areas may develop with growth of bones. In adults, on the contrary, these areas may disappear.

While this condition is not of clinical importance it is an interesting one of speculative nature. No treatment is required and the prognosis is favorable. It is included here because it might conceivably be confused with areas of osteoblastic metastasis from prostatic cancer if only a few areas are seen in a flat bone such as the innominate. When found in the small bones of the hands and feet it presents a clear picture that is pathognomonic (see Fig. 373).

HURLER'S SYNDROME (GARGOYLISM)

This condition occurs predominantly in males. It is familial in nature and unusual features are first noted at about the age of 3 years. The long bones

are thickened and there are shallow acetabular and glenoid fossae. The head is usually enlarged and may be either scaphocephalic or brachycephalic. The prominent features are a flattening of the bridge of the nose



FIG. 375. Hurler's syndrome (gargoylism).

and fullness of the cheeks. The hands are clawlike. Microglossia is present together with corneal clouding or retinitis pigmentosa. Deafness occurs quite frequently. In this condition the midpoint of the body is near the normal position as distinguished from achondroplasia where the mid-point is near the umbilicus (short legs). Mental retardation is present but sexual characteristics are fully developed.

The abdomen is quite prominent and usually there is an umbilical hernia. The spleen and liver are markedly enlarged and both organs are usually so mobile that they may be picked up between the hands. Characteristically, the liver shows cirrhosis and in the late stages of the disease it shrinks to about the size of a grapefruit. Death occurred in 1 case and was found to be due to malnutrition and cirrhosis (see Figs. 374-377).

MELORHEOSTOSIS

The peculiar bone affection first described in 1922 by Joanny and Leri is characterized by irregular periosteal and cortical swelling involving a



FIG. 376. Hurler's syndrome (gargoylism).



FIG. 377. Gargoylism. Note shallow acetabula; also misshapen femoral heads.

considerable extent of the shaft of long bones and presenting an appearance on the roentgenogram which has given rise to its name—like flowing honey or candle wax. Several bones of an extremity are usually involved and in a manner to suggest to earlier observers that the process must be related to the nervous system or to a metamerie disturbance in embryologic development. While in most of the reported cases bones of a single extremity have been involved, there are examples in which ribs and even the skull and mandible have been affected; 1 case with bilateral lesions was described in 1942 by Franklin and Matheson. Males are more often subject to the disease than are females. Heredity has not been established as a factor.

Widman and Stecher reviewed the literature in 1935 and attempted a classification into four groups according to the "flow" of the bone proliferation, i.e., (1) the complete continuous type, (2) the partial continuous type, (3) the interrupted type, and (4) the circumscribed type. The clinical significance or practical importance of this classification is not apparent.

SYMPTOMS, SIGNS, AND LABORATORY FINDINGS

The onset of symptoms of pain, tenderness, and limitation of motion in joints adjacent to the involved bone is insidious although seldom severe or incapacitating. Physical signs may be scarcely noted since bulky swellings are unusual.

Noteworthy is the absence of any abnormal blood-chemistry findings. In a case seen at Harmon General Hospital, serum calcium, phosphorus, phosphatase, blood sugar, NPN, serology, and leucocyte count were all within normal limits.

ROENTGENOGRAPHIC FINDINGS

The appearance of the lesion as seen on roentgen-ray examination is the most valuable means of diagnosis and its principal features have been briefly described above. A case involving the upper extremity is illustrated in Figure 378.

DIAGNOSIS

Unless a complete roentgenographic examination is made films of an isolated lesion may not be diagnostic and the area may be mistaken for lues, osteoid osteoma, sclerosing osteitis, or even for an ancient healed periostitis of pyogenic origin. With the absence of any positive laboratory findings, and with the demonstration of areas in several bones confined to one extremity in which the classical melted-tallow appearance is evident, the picture is sufficiently clear-cut to permit one to make the correct diagnosis.

PATHOLOGY

The gross appearance suggests a benign process. No case of malignant sequelae has as yet been reported. Five cases in the literature have had

biopsies. The histologic appearance is notable for the marked thickening of the lamellae with bizarre osseous formations and a general reduction in the osteoblastic elements.

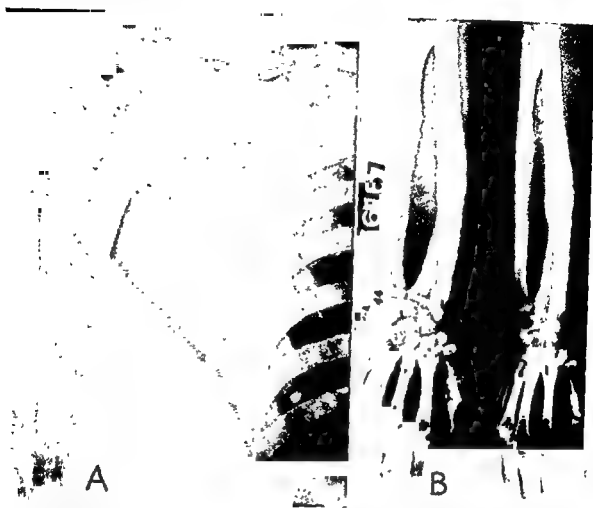


FIG. 378. Melorheostosis. *A*, Note changes confined almost entirely to the lateral side of the humerus. These consist of a sclerosing process which must be distinguished from Albers-Schönberg disease or from a sclerosing osteitis of Garré type. *B*, Same case. Note the involvement confined to the radius and the carpal and metacarpal bones on the radial side. This arrangement gives support to the metameric theory of origin of this condition. (Harmon General Hospital, Longview, Texas.)

TREATMENT

No specific therapy has been suggested. The disease is probably slowly progressive and self-limited. Until more is known of its etiology, all treatment must be considered as unsatisfactory. Surgical attack might envisage resection or excision of areas in which a replacement by bone graft is feasible. Thus far, however, there has been no precedent for such procedure and in order to justify it one would have to encounter more disabling symptoms than have thus far appeared in reported cases.

PROGNOSIS

The prognosis is favorable. No case has as yet been reported as coming to autopsy. In view of the author's belief, however, that secondary malignancy

nant changes tend to occur in abnormal bone, such an event would not be surprising. It would seem that all cases of this uncommon skeletal abnormality should be observed at regular intervals over an indefinite period of



Fig. 379. Senile postmenopausal osteoporosis. Note especially the changes in the vertebrae with compression and scoliosis.

time. Failure to recognize it as a distinct clinical entity has in all probability resulted in some cases being overlooked. It is likely that examples will be reported more frequently in the future.

OSTEOPOROSIS

Osteoporosis is a term which is used rather loosely at times and which ought to be restricted. It is a condition quite distinct from osteomalacia—caused by failure of mineralization of bone—and from hyperparathyroidism where calcium is withdrawn from bone. It should not be confused with polyostotic fibrous dysplasia where bone destruction is increased. Rather the term should be reserved for those cases in which the primary disturbance is lack of formation of matrix due to hypofunction of osteoblasts.

In practice one sees osteoporosis in association with atrophy of disuse, in old age, malnutrition, in the postmenopausal patient (see Fig. 379), in Cushing's syndrome, and acromegaly. Occasionally cases are encountered in which there is no satisfactory explanation of the osteoporosis and these must still be classed as idiopathic.

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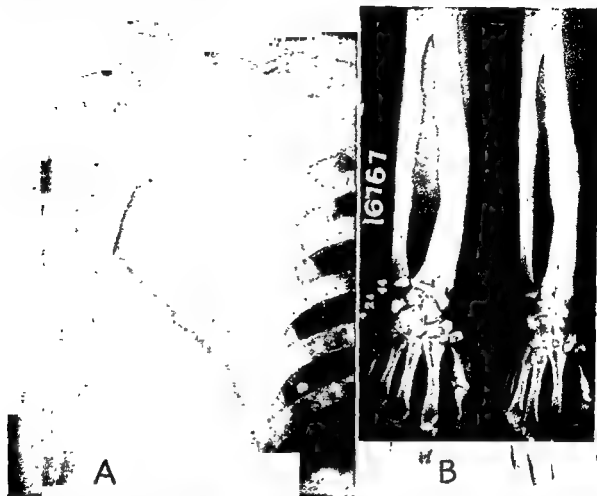


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humerus during the ensuing twelve years. At no time was the skin broken nor was there any suppuration or fistula. It is recorded by Gross (*Textbook of Surgery*) that the patient "could readily raise a weight of 100 pounds" and, according to Jackson, "he could hoe, rake, shovel, sweep, cut wood, carry a large pail of water, hold a knife at the grindstone and write a good hand." Costello, in his *Encyclopedia of Practical Surgery*, published in 1841, referred to the case as "unparalleled in the records of surgery."

The patient lived for 50 years and died of pneumonia at the age of 70. The limb was dissected postmortem by Professor Thomas Dwight of Harvard (the specimen is still in the Warren Museum). A description of the findings was written by C. B. Porter and published, together with all the details of the case, in the *Boston Medical and Surgical Journal* in 1872. Roentgenograms of the specimen taken by Sosman showed only three thin spicules of bone remaining in the humeral area.

The second case was reported in 1933 by Thoma. The patient, a 36-year-old housewife, developed progressive absorption of the facial bones. In the case of the mandible, the disappearance was complete; the maxilla, palatine and sphenoid bones were similarly affected but to a lesser degree. Her ailment came on during the fifth month of her third pregnancy and followed teeth extractions made necessary by dental sepsis. Roentgenograms showed the other bones to be normal. Thoma called attention to the fact that the involvement was that of the distribution of the fifth cranial nerve; he suggested that it might be a neurotrophic atrophy. There was no evidence of hyperparathyroidism.

Jackman, in 1939, reported a case of spontaneous absorption of bone. The patient, a male aged 21 years, first consulted a physician in January 1932, for pain in the right hand which had been noticed after woodchopping performed two weeks previously. The roentgenogram revealed a remarkable narrowing of the shaft of the middle metacarpal. The patient then disappeared for a period of four years and ten months. On his return, examination revealed marked deformity associated with nearly complete absence of the middle metacarpal and a patchy erosion of the os magnum. The finger was useless and was amputated. The pathologist of the Bristol Royal Infirmary reported that the condition "conformed most closely to fibrocystic disease." The phalanges were normal. Two years later Jackman reported that the fourth metacarpal showed signs of the same process. A blood calcium and Wassermann test were not revealing.

He reported a third case in 1945. His patient was a 20-year-old Negro who followed a mild trauma to the left shoulder during which time later revealed marked absorption. The complaint was inability to raise his left arm

DIAGNOSIS

Osteoporosis requires consideration as an alternative diagnosis in certain cases of widespread metastatic cancer. It must therefore be borne in mind when one encounters lytic changes in a patient with no demonstrable primary tumor. Such cases should be carefully investigated for evidence of one or more of the conditions which are associated with osteoporosis and which have just been enumerated. In this investigation the assistance of the chemical laboratory may be of great value.

If practical an aspiration—or even an open—biopsy may be employed and should be of help in establishing or disproving a metastatic basis for the bone changes. Obviously the opinion of the roentgenologist will be obtained and evaluated in connection with the other clinical and laboratory findings.

TREATMENT

In senile osteoporosis especially the administration of steroid hormones is helpful. Reifenstein and Albright treated a large group of cases with estrogens alone and combined with testosterone compounds, and they report gratifying results as measured by a lessening or disappearance of pain in the spine or other bones. These authors are less certain that pre- and post-treatment roentgenograms establish positive evidence of increased calcification.

There is at least a possibility that prolonged estrogenic treatment may cause cancer and this must be borne in mind. Moreover, since many of the steroids cause retention of sodium, testosterone therapy may give rise to edema in older patients, particularly if their serum protein level is low.

Immobilization is undesirable since it superimposes the factor of disuse atrophy.

SPONTANEOUS ABSORPTION OF BONE (PHANTOM BONE—DISAPPEARING BONE)

A little-understood and extremely rare condition affecting bone has been described under various terms of which perhaps *acute spontaneous absorption of bone* is the most appropriate, although *phantom bone* or *disappearing bone* is sometimes used to describe it. The rarity of this entity can best be appreciated when one realizes that prior to 1946 only 3 examples were reported.

The earliest case, reported briefly in the *Boston Medical and Surgical Journal* in 1838, was that of an 18-year-old male who had sustained three successive fractures of the right humerus in a period of two months. There was no tendency to unite but on the contrary a steady absorption of the

humerus during the ensuing twelve years. At no time was the skin broken nor was there any suppuration or fistula. It is recorded by Gross (*Textbook of Surgery*) that the patient "could readily raise a weight of 100 pounds" and, according to Jackson, "he could hoe, rake, shovel, sweep, cut wood, carry a large pail of water, hold a knife at the grindstone and write a good hand." Costello, in his *Encyclopedia of Practical Surgery*, published in 1841, referred to the case as "unparalleled in the records of surgery."

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Branch reported a third case in 1945. His patient was a 20-year-old Negro soldier whose symptoms followed a mild trauma to the left shoulder during basic training. It seems likely that the process had commenced prior thereto since roentgenograms taken a short time later revealed marked absorption of bone. The patient's only complaint was inability to raise his left arm

DIAGNOSIS

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The chest film and laboratory findings, including cytology, serology, and blood chemistry, were all normal. The author had an opportunity to see this case in consultation with Major Branch at Harmon General Hospital, and he kindly permitted reproduction of the roentgenograms (see Fig. 380).

In addition to the 3 reported cases there are several other similar ones that have not been published. Branch refers to one which was presented at the Clinical Orthopedic Society in Cleveland, Ohio. The patient was a young woman with involvement of the scapula, which during a five-year period of observation completely disappeared. The bone was replaced by connective tissue. The laboratory studies, as in Branch's case, were all normal.

Another case was observed at the Presbyterian Hospital, New York, by Murray and Smith, to whom I am indebted for the details and for permission to reproduce the roentgenograms.

CASE REPORT

The patient, a 41-year-old white female, dated her history back to 1928, when she tried to catch a child falling out of a chair. Following this she had slight discomfort for several weeks. Two weeks later she lifted a cake of ice. X-ray showed fracture of the clavicle at the junction of the middle and inner thirds. She returned to work in 1929 having no difficulty in using her arm. In January, 1930, she again felt a slight pain on raising her arm. X-ray examination showed an absence of the outer two-thirds of the right clavicle. She continued to work. In November, 1930, X-ray examination showed beginning absorption in the right scapula. In December, 1933, the clavicle had completely disappeared and a beginning absorption was noticed in the right first rib. She continued to work as a housekeeper.

She was operated upon in January, 1935, and the remaining portion of the scapula removed for biopsy. Her parathyroids were also explored and she had a non-toxic goitre removed at the same time. In June, 1935, Murray excised the remainder of the first rib. Pathological examination of the bone removed showed queer changes but no definite diagnosis could be made. In September, 1935, the patient had a massive sero-sanguinous effusion in the right chest associated with dyspnoea and precordial pain.

She died on October 1, 1935. An autopsy was performed and a diagnosis of pulmonary thrombosis and chronic endocarditis was made.

The third unreported case, a patient of Ehler and Wright of Albany, conforms quite closely to the pattern of Branch's and Murray and Smith's cases. The patient was a 17-year-old boy who fell and fractured the right clavicle in November, 1943. Several months later the right shoulder began to droop and weakness and pain were noted in the right shoulder girdle. Six months after the fracture, X-ray films revealed absence of the entire right

above his head. Films taken over a five-month period disclosed progressive loss of the clavicle, acromion process, and the supraspinous portion of the scapula as well as part of the neck of this bone.

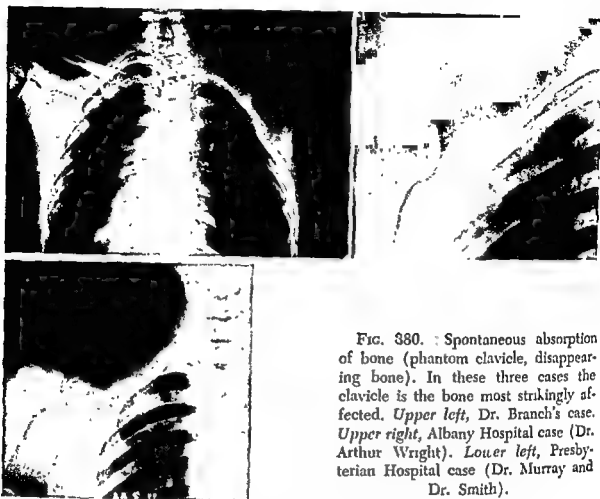


FIG. 380. : Spontaneous absorption of bone (phantom clavicle, disappearing bone). In these three cases the clavicle is the bone most strikingly affected. *Upper left*, Dr. Branch's case. *Upper right*, Albany Hospital case (Dr. Arthur Wright). *Lower left*, Presbyterian Hospital case (Dr. Murray and Dr. Smith).

Biopsy material taken from the area where the bone had disappeared was reported by Lt. Col. Stuart Lippincott as follows:

Sections taken through muscle, fat and connective tissue show no evidence of any vascular inflammatory or neoplastic disease.

Sections through what appeared to be the medulla of the bone showed almost complete absence of bone spicules. There are abundant remaining vascular channels from the medullary portion, and they contain red blood cells in scattered areas. Outside of these channels there is a small amount of hematopoietic tissue. There is only one area showing the presence of fibrosis. There is no evidence of an inflammatory or neoplastic process in these sections.

Sections through actual bone show the presence of many well-formed spicules. There are definite areas of degeneration in the bone with the presence of osteoclasts and localized fibrosis. At the junction of bone and cartilage, there is an irregular area of osteoid tissue as well as fibrosis.

The chest film and laboratory findings, including cytology, serology, and blood chemistry, were all normal. The author had an opportunity to see this case in consultation with Major Branch at Harmon General Hospital, and he kindly permitted reproduction of the roentgenograms (see Fig. 380).

In addition to the 3 reported cases there are several other similar ones that have not been published. Branch refers to one which was presented at the Clinical Orthopedic Society in Cleveland, Ohio. The patient was a young woman with involvement of the scapula, which during a five-year period of observation completely disappeared. The bone was replaced by connective tissue. The laboratory studies, as in Branch's case, were all normal.

Another case was observed at the Presbyterian Hospital, New York, by Murray and Smith, to whom I am indebted for the details and for permission to reproduce the roentgenograms.

CASE REPORT

The patient, a 41-year-old white female, dated her history back to 1928, when she tried to catch a child falling out of a chair. Following this she had slight discomfort for several weeks. Two weeks later she lifted a cake of ice. X-ray showed fracture of the clavicle at the junction of the middle and inner thirds. She returned to work in 1929 having no difficulty in using her arm. In January, 1930, she again felt a slight pain on raising her arm. X-ray examination showed an absence of the outer two-thirds of the right clavicle. She continued to work. In November, 1930, X-ray examination showed beginning absorption in the right scapula. In December, 1933, the clavicle had completely disappeared and a beginning absorption was noticed in the right first rib. She continued to work as a housekeeper.

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clavicle and second rib. Ten months later (March, 1945) the films demonstrated extensive destruction of the right scapula, head and neck of humerus, upper three ribs, and sixth and seventh cervical vertebrae with partial collapse of the seventh. Blood-chemistry studies were made at this time and



FIG. 381. Dr. Branch's case. Notice loss of shoulder motion, due to absence of acromium process and clavicle.

were normal. Later involvement was noted of the fifth cervical and the upper three thoracic vertebrae associated with a right hemothorax. Soon the character of the fluid changed from bloody to chylous and after a gradual decline the patient died twenty-seven months after the initial injury. At autopsy the apparent cause of death was an infected pleural effusion on the right due to hemolytic staphylococcus aureus with an extensive mediastinitis and cellulitis of the right axilla and posterior cervical region. The essential bony lesions included the right scapula and the lower cervical and upper thoracic vertebrae, many of which were transformed into multicystic bony shells. The right clavicle and upper three ribs were completely absorbed (see Figs. 383-388). Both brain and spinal cord were removed and showed no abnormality.

Finally, a case recently reported by King might be considered as a possible example of this condition although there are certain differences in the microscopic appearance and the process involves the lower extremity while all but one of the preceding cases have been of the shoulder girdle. In this patient, an 11-year-old white boy, the lesion began in the lower femur and progressed following amputation at mid-thigh to affect the femoral head and neck, the acetabulum and the iliac bone above it. The only deviation from normal laboratory studies was the elevated serum alkaline phosphatase of 18.2 Bodansky units. Kalmer, Kahn, and tuberculin tests were negative. All other bones were roentgenographically normal. The pathologist's report was as follows:

Examination of the specimen showed that the subcutaneous tissue in the region of the discolored skin was indurated and stained with blood pigment. The fascial layers and the septa were indurated, giving rise to continuous long, white strands of varying thicknesses. This condition extended from the subcutaneous tissue down to the bone, and involved the periosteum. Surrounding the large vessels, these strands were so fine and thin that they gave the appearance of spider-webbing. Between the muscles the strands were thicker, often reaching

the size of small vessels or nerves. The bone was markedly porous and broke easily. It had the appearance of bone which had been decalcified by soaking it in a solution.



FIG. 382. Dr. Branch's case. Section through area that should have been medullary portion of the clavicle ($\times 16$).

The microscopic section of the femur showed considerable osteoporosis. The number of capillary blood vessels was greatly increased. This was most evident where the trabeculae were thin and widely spaced. The soft-tissue sections showed fibrous tissue and thin-walled blood vessels.

Eleven months after the amputation a second operation was performed, this time on the left groin. Tissue examination was reported as follows: "Microscopically, the section showed an increased number of blood vessels, but they contained very little blood; their walls were thin, but development appeared to be normal. There was extensive fibrosis in the surrounding

clavicle and second rib. Ten months later (March, 1945) the films demonstrated extensive destruction of the right scapula, head and neck of humerus, upper three ribs, and sixth and seventh cervical vertebrae with



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FIG 383. Drs. Bickel and Broders' case. Roentgenogram made on September 28, 1942, showing the onset of the lytic process in the left ilium



FIG. 384. Same case as FIG 383. Roentgenogram made on December 2, 1943, showing almost complete absence of the left ilium, with collapse of the pelvis on the left.



FIG. 385. Same case. February 18, 1914, showing the pelvis after the patient had received the first course of roentgen therapy and traction; the pelvic outlet has been restored somewhat.



FIG. 386. c

areolar tissue. The most striking feature, however, was the focal aggregation of lymphoid cells, sometimes grouped about well-organized germinal centers.



FIG. 387. Same case. August 8, 1945, showing extension of destruction to the sacrum and the fourth and fifth lumbar vertebrae.

The sections were submitted to four distinguished pathologists and all considered the lesion to be some type of angioma. One expressed the view that though neoplasm can be ruled out the nature of the lesion was obscure and King closes with the remark that "a satisfactory diagnosis for this puzzling case has not been established."

Another case of interest in connection with these foregoing examples of spontaneous absorption of bone is that of Bickel and Broders which concerned a girl who began to limp at the age of $3\frac{1}{2}$ years. Her birth and early infant period had been entirely normal. Films of the pelvis revealed an osteolytic process which involved the left ilium (see Fig. 383); serial roentgenograms showed a steady progressive destruction of the left iliac bone and gradual involvement of the sacrum, fourth and fifth lumbar vertebrae, and possibly of the trochanteric region of the left femur (see Figs. 383-7). Disability during the four-year course was progressive but pain was practically nonexistent.

Biopsy was reported as lymphangioma, infiltrating fat, fibrous tissue, and muscles; bone and cartilage portions of the biopsy were unsatisfactory for study.



FIG. 388. Same case. September 23, 1946, showing pelvic deformity and extension of the erosion.

Roentgen therapy was given without benefit and discontinued because the lesion seemed not to be radiosensitive.

This is apparently the first recorded case of lymphangioma of bone, and the element of doubt as to whether it began as a primary bone neoplasm or secondarily involved the ilium by erosion or direct extension remains unanswered.

One is struck by the similarity of this case to others mentioned as examples of "disappearing bone" or "spontaneous absorption of bone" on every ground except that of the histology, in the other instances there was no suggestion of either an inflammatory or a neoplastic process whereas in the case of Bickel and Broders it appears to have been due to benign neo-

plasm of a type which has not been previously recognized as occurring primarily in bone.

If one attempts to depict the features of these remarkable cases in order to describe a syndrome the following points are noteworthy.

There is nothing to suggest that the basis for the bone changes is either neoplastic or infectious. It is difficult to explain how a metabolic disorder could affect a single portion of the skeleton and leave the other bones undisturbed.

The influence of antecedent injury as an etiologic factor is suggestive. Yet it seems probable that the lesions antedated the trauma and that it only served to call attention to them. The predilection for those portions of the shoulder girdle nearest the trunk is striking; the clavicle was the most frequently involved bone early in the disease. Extension of the process to adjacent ribs and vertebrae, as well as to the scapula and proximal portion of the humerus, is a prominent feature. No explanation can be offered for the intrathoracic complications which served to terminate fatally the course of the Presbyterian and Albany Hospital cases.

The gross and microscopic features give us little assistance in explaining the nature of this obscure disease. Bone is apparently absorbed and replaced by fibrous tissue and no other specific features are presented.

Therapy has not been successful in influencing the course of the disease and indeed has not been tried save in King's case where amputation was followed by progress of the disease in the stump, but subsequent roentgen therapy seems to have had a favorable effect. In the other cases surgery has been limited to biopsy.

Until more is understood about the underlying cause of this process, therapy cannot be placed on a sound foundation. The existence of other unreported cases is probable and they should be recorded. All cases should be followed carefully, and in those that succumb complete postmortem studies should be made. Blood-chemistry findings have offered no clue. A summary of the reported cases is given in Table LIII.

INFANTILE CORTICAL HYPEROSTOSES

In 1945 Caffey and Silverman described four examples of a syndrome which usually occurs in the early months of the first year of life, and which is characterized by soft-part swellings that are tender, a febrile reaction that is inconstant and irregular, and striking bone changes. The etiology is unknown, and the pathogenesis obscure. The process seems self-limited and runs its course apparently uninfluenced by therapy. One year later Caffey reported six additional cases. Smyth recognized this syndrome independently and reported cases under the title: *Periosteal Reaction, Fever and Irritability in Young Infants: A New Syndrome?*

TABLE LIII
SPONTANEOUS ABSORPTION OF BONE

CASE	YEAR	SEX	AGE	BONES INVOLVED	TRAUMA	BIOPSY	OTHER SURGERY	ROENTGEN THERAPY	COMPLICATIONS	MICROSCOPIC	CHEMISTRY	OUTCOME
Boston case quoted by Costello Thoma	1838			Humerus	Followed two fractures							Died (autopsy)
Branch	1933	M	20	Facial bones; complete absorption of mandible	Mild, questionable	Yes	No	No	None	Fibrous tissue	Normal	No prolonged follow-up
Cleveland Case quoted by Branch	1945	F		Clavicle, scapula	Not stated	Yes	No	No		Fibrous tissue		End-result not known
Murray & Smith Presbyterian Hosp., NY City	1934	F	41	Clavicle, 1st scapula, 1st rib	Mild, questionable	Yes	No	No	Hemothorax, pulmonary thrombosis, endocarditis	Queer bone changes; no definite diagnosis made		Died (autopsy)
Ehler & Wright Albany Hosp.	1943	M	17	Clavicle, humerus, cervical & dorsal vertebrae, ribs	Fracture	Yes	No	No	Emphysema, cellulitis of axilla & neck, mediastinitis	Fibrous tissue	Normal	Died (autopsy)
King University of Pa. Hosp.	1941	M	11	Femur, hum	Fall from bicycle	No	Primary amputation	Yes	None	Fibrous tissue, thinwalled blood vessels	Elevated serum phosphatase	Improved after roentgen therapy; cured?

CLINICAL FEATURES

The condition is characterized by tender, soft-part swellings of the face, neck, chest, and extremities. The long bones of the extremities, mandible, clavicles, scapulae, ribs, and calvarium have been affected. Symptoms have their onset as early as the third week and as late as the twelve months of life. Trauma is apparently not a factor. Syphilis, rickets, and scurvy seem clearly excluded in all cases.

ROENTGENOGRAPHIC APPEARANCE

The lesions in the bones were multiple in all but one of Caffey's cases. They were characterized by external thickening of the corticalis while the medulla, the metaphysis, the epiphyseal plates, and the centers of ossification in the epiphyses appeared to be unaffected. The roentgenographic appearance prompted Caffey to apply the term *infantile cortical hyperostosis*.

LABORATORY FINDINGS

Serologic tests for syphilis have been negative. Bacteriologic findings do not suggest that the condition is due to an infection by any of the common organisms. Examination of the blood does not show evidence of hemorrhagic disease. Biopsies reveal only hyperplasia of bone with no features of inflammation or subperiosteal hemorrhage.

We have observed four cases of this disease in children aged 3, 3, 4 and 7 months respectively. The lesion was monostotic in every instance. In three cases the scapula was the affected bone while in the fourth the mandible was involved.

In the three scapula cases the diagnosis of primary malignant tumor of bone was seriously considered; two of these had been subjected to previous biopsy elsewhere and the pathologists had regarded them as osteosarcoma. One case was biopsied at Memorial Hospital. In none of these cases did the sections that were reviewed by our pathologists considered suggestive of a neoplastic process.

It appears advisable, in the light of our experience, to call attention to this condition as one which may, in its monostotic form, require consideration in the differential diagnosis from malignant bone tumors in the newborn and in infants.

TIETZE'S DISEASE

There have been about 20 reported cases of symptomless nonsuppurative, nonspecific swellings of rib cartilages. This peculiar condition has been called Tietze's disease.

We have in the past two decades encountered a group of these cases without realizing that they had been described as a distinct entity. Cases are usually seen because of the presence of a painless swelling over



FIG. 389. Infantile cortical hyperostoses involving the left scapula.

costal cartilage of a single rib. Nothing of note is seen on roentgenographic examination. Histologic study of material removed surgically reveals no specific process that can be identified and the nature of the condition remains obscure.

Most of the cases we have seen were in school-age children and were referred by school physicians or district health officers on suspicion that a bone tumor of the rib was present. No treatment is required and the prognosis is excellent.

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CONDITIONS DUE TO BONE INFECTION

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SECTION ELEVEN

Miscellaneous

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72. PATHOLOGIC FRACTURE

THE UNFORTUNATE COMPLICATION OF PATHOLOGIC FRACTURE OCCURRING in a primary malignant bone tumor is a matter of serious import and adds considerably to the difficulties of the patient and the attending physician. A similar situation exists when the fracture occurs in a metastatic bone lesion, although here the outlook, regardless of fracture, is hopeless as far as recovery is concerned.

In benign tumors as well as in many nonneoplastic conditions of bone, a pathologic fracture is a troublesome complication and may affect adversely the final functional result. In some specific conditions, notably unicameral or solitary bone cyst and central chondroma of phalanx, the fracture may be the first symptom of underlying bone pathology. In these cases displacement is often negligible and may not interfere with the ultimate result.

The presence of plasma cell myeloma or metastatic carcinoma may not be suspected until a pathologic fracture occurs. Any fracture sustained after a trivial trauma should therefore arouse suspicion of preexisting pathology. Sarcoma rarely arises after a simple fracture through normal bone. A critical examination of the immediate roentgenograms will nearly always reveal some alteration in the normal texture of bone at the site of fracture. Pain may have been present in mild degree prior to the fracture and mild "neuritic" or "myalgic" complaints can be elicited after careful questioning.

However, a few cases have been recorded and others have been personally observed in which the original roentgenograms made immediately after injury have appeared to indicate a simple fracture without recognizable evidence of underlying disease of bone. Later, when the obvious nature of the pathologic fracture was apparent, a review of the original films revealed disease which had escaped the attention of the roentgenologist as well as the surgeon. Nevertheless, Bloodgood, Codman, and William B. Coley observed and reported cases totaling 10 in number in which sarcoma apparently did arise at the site of a simple fracture. The author has seen 1 striking case in which Ewing was convinced that the sarcoma actually arose

3. Primary Malignant Tumors of Bone

As Sharp and the author have pointed out, the occurrence of pathologic fracture in cases of *osteogenic sarcoma* must be regarded as of serious significance. Comparing 59 unfractured cases with 14 that had fractures, the latter showed an average duration of life that was almost ten months shorter. There are two possible explanations: (1) the rapidly growing osteolytic form which is responsible for most of the pathologic fractures is a tumor of high malignancy as judged by histologic criteria; (2) the occurrence of fracture naturally tends to open up vascular channels and favors wide dissemination. Prompt amputation is indicated for pathologic fracture in *osteogenic sarcoma* although it is seldom successful in controlling the disease.

For endothelioma the use of roentgen therapy with support of the limb in removable plaster casings is appropriate. However, survival for five years or more has not been observed in a single case complicated with pathologic fracture.

Reticulum cell sarcoma and liposarcoma require similar therapy, i.e., irradiation and, if uncontrolled, amputation.

Myeloma is frequently associated with fracture and while irradiation may result in healing of the fracture the ultimate outlook remains hopeless.

4. Metastatic Carcinoma of Bone

This group gives rise to the greatest number of pathologic fractures. In an individual who is past the age of 36 the likelihood is strong that a pathologic fracture is traceable to myeloma or to metastasis from cancer of the kidney, thyroid, breast, or some other organ. Palliative roentgen therapy is the only therapeutic measure available although in breast or prostatic cancer, hormone therapy or castration is often of pronounced benefit. In metastatic disease of the vertebrae with pathologic fracture it is important to apply spinal braces to prevent or minimize the effect of collapse. Such support is essential during the period when roentgen therapy or hormone treatment is being administered.

PROGNOSIS

Healing of the fracture may follow roentgen therapy, particularly if the lesion that caused the fracture is radiosensitive and the dosage employed is insufficient to interfere with bone repair. Occasionally spontaneous union may be observed; this is usually of short duration and is followed by further destruction and refracture. In most instances where pathologic fracture is due to metastatic carcinoma the beneficial effect of irradiation is not striking as regards stimulation of bone repair and healing of the fracture. If the patient survives for a considerable period, refracture is prone to occur.

73. MEDICOLEGAL ASPECTS OF TRAUMA IN TUMORS OF BONE

A REVIEW OF THE VOLUMINOUS LITERATURE DEALING WITH THE QUESTION of injury as a causative factor in the development of malignant tumors in general and of tumors of bone in particular leaves the reader convinced that from the mass of conflicting opinions and theories expressed it is difficult, if not almost impossible, to reach an unbiased conclusion.

We are not concerned here with any of the so-called chronic irritations of occupation, such as chimney-sweep cancer or mule-spinner's cancer. We are interested only in the relationship of direct trauma as a theoretical causal factor in the development of sarcoma of the musculoskeletal system.

The question of whether a malignant bone tumor which developed or was first recognized after an injury to the part was caused by that injury is one that has been argued for many years. While in earlier times this was a matter merely of academic interest, with the advent of Workmen's Compensation legislation and liability insurance the whole question has taken on great medicolegal importance.

Unquestionably the majority of those of the medical profession who conceded a causal relationship of injury to bone sarcoma have been clinicians while the opponents of this view have, for the most part, been pathologists. The trend of opinion in recent years has been to doubt the importance of a single trauma; those who still accept it are in the minority. After many years of experience in the field of bone tumors, the author must confess to an uncertainty of opinion and to a feeling that the final answer has not as yet been provided. He does not hold that a single injury cannot ever be a factor of etiologic significance. He feels that a study of the histories of a large group of cases of bone sarcoma leaves one with the inescapable impression that in a high percentage of cases—50 per cent in some types of tumor—recent local injury antedated the demonstrable appearance of the tumor. Does this have significance? Was it merely a coincidence or did the injury call the patient's attention to a pre-existing tumor, i.e., *traumatic determination* (Ewing)?

Obviously it is human nature for the layman to ascribe a malignant

tumor to an antecedent local injury even though there may be no material gain or selfish interest at stake. On the other hand, everyone during the course of life sustains injuries, some of which are of even greater severity than those cited as being responsible for a bone tumor. Therefore, injury cannot be regarded as the *sole* causative factor. The exceeding rarity of late sarcomatous development following so serious an injury as a major long-bone fracture is an argument that has often been advanced by the opponents of the *traumatic* theory (see Chap. 72, "Pathologic Fracture"). If one examines carefully those cases in which a sarcoma appears to have developed following a fracture through bone that is apparently normal it is generally possible to detect pathologic changes already present at the site of the fracture. In some instances these fractures may unite and the true nature of the process may not be apparent for some months or even years. It seems highly probable therefore that the incidence of malignant tumors arising on the basis of simple fracture is exceedingly rare. While we know of no such case in the records of Memorial Hospital it cannot be categorically stated that it never occurs; in fact we have seen 2 cases in other hospitals which on careful scrutiny would seem to be authentic examples.

In 1907 at the French Congress of Surgeons, Segond outlined certain conditions which he felt must be fulfilled for the establishment of a causal relationship between an antecedent local injury and a subsequently developing malignant tumor. They include the following:

1. That there was a verified trauma
2. That it was of sufficient severity
3. That reasonable evidence existed of the integrity of the part prior to the injury
4. That the site of the injury corresponded to that of the tumor
5. That the tumor appeared at a date not too remote from the time of the accident to be reasonably associated with it
6. That the diagnosis was confirmed by clinical, roentgenographic, and, whenever possible, microscopic examination

These criteria have been widely accepted both in Europe and in America as a basis for adjudication of disputed claims. In actual practice, however, they are very seldom verified and the fact that they exist is an incentive to a clever lawyer or doctor, who is financially interested in the case, to "trump up" stories and manufacture evidence to conform to these criteria. Commenting specifically on criterium 2, i.e., sufficient severity of the trauma, we regard this as most vague. Apparently no one knows how severe or trivial an injury must be to be regarded as the theoretical cause of a cancer. One almost has to adopt as a working hypothetical possibility the theory that any trauma of any sort and of any degree of severity may cause

any sort of cancer in any location. In other words, there seems no clear way to quantitate the amount of trauma that is necessary to cause cancer. It is worthy of note that in the majority of claims filed in the Compensation Courts of New York the injury to which the tumor was ascribed has been trivial; seldom has there been any evidence of a major alteration of the part concerned.

The author feels that in many medicolegal cases in the past injury as a determining factor has been overemphasized and that decisions have been rendered on a flimsy structure of scientific evidence. It is believed that at present the system in vogue whereby medical expert testimony is given is shocking in several particulars and is rendered less valuable by the undeniable fact that the expert would not have been called to testify had his views not been known in advance and his opinion anticipated as being favorable. Until the present set-up is revised and all experts are called, employed, and recompensed by the Court rather than by the plaintiff or the defendant, real experts will shun medicolegal cases and the evils of the present day will continue unabated.

In the interest of fair play, to assure a complete clinical record, to avoid important blanks in the sequence of a given history, it should be the inviolate rule that whoever takes the initial history of a patient with a suspected sarcoma should set forth certain pertinent facts in the records. First of all he should ask the patient to what *he* attributes his tumor and, if the latter describes an injury, he should then be asked whether the cause has been suggested to him by others. The history should contain the following facts:

1. Date of injury
2. Nature and mechanism of injury
3. Site of injury
4. Subsequent manifestations of injury, e.g., ecchymosis, swelling, tenderness, disability
5. Period following injury in which these symptoms persisted
6. Interval between subsidence of symptoms and signs of injury and first recognition of symptoms or signs of tumor

In addition a complete clinical record should include roentgenograms of the part concerned taken as soon as possible after the injury as well as others taken subsequently. Wherever possible microscopic confirmation of the diagnosis should be sought.

AGGRAVATION

The provisions of the Workmen's Compensation laws of many states presume that an injury is compensable which can be construed as having aggravated a preexisting malignant tumor. Therefore, claims of aggravation are often made, and this introduces a much more controversial issue. From

what is known of the dissemination of malignant cells it is probable that direct trauma to the primary lesion might be conducive to metastasis. However the only experimental evidence on single trauma in tumors of known dissemination rate fails to support this viewpoint, and the fact remains that malignant tumors do metastasize with or without local trauma. It has seemed to the author that in a given case one would have to show that the clinical course of the disease had been adversely affected by the trauma, i.e., that it ran a much more rapid course than the average untraumatized case. Even then one must realize that there is a great natural variation in the rapidity of spread and total duration of malignant tumors. It would appear therefore that if a sarcoma were accepted as having existed prior to injury the circumstances of its course thereafter would have to be exceptional before one could justifiably assume aggravation.

Decisions in these accident cases that are adverse to the workman or to the injured plaintiff frequently entail severe hardship to the individual or his family. In an effort to avoid any possible injustice to the injured party, the doctor is apt to let his sympathies color the medical testimony which he offers. This motive seems also to influence the referee, the jury, and sometimes even the judge. Yet as Stewart has pointed out, this is no excuse for making awards in the face of incompetent evidence or of using "supposedly scientific medicine to further his notion of proper social behavior."

Stewart illustrates the faulty reasoning of the "supposed expert" as follows: "The same surgeon who will do all sorts of orthopedic jobs involving chiseling into bone or insertion of such objects as ice tongs or pins or screws may testify that a blow which has left no real signs has caused an osteogenic sarcoma, although he never thinks his surgery will do so nor has he ever warned a patient with the severest form of bone trauma—a fracture—to be on the lookout for a possible sarcoma."

Such arguments bear much weight and are hard to refute.

There are certain bone processes and benign lesions in which the role of trauma seems more difficult to deny. Of these the most conspicuous is benign giant cell tumor of bone. Considerable authoritative opinion upholds the theory that this tumor is commonly caused by the effects of trauma (see Chap. 17). Many patients with giant cell tumor have been awarded compensation, and we believe rightly so. On the other hand, it should be pointed out that pathologists who have had considerable experience in bone neoplasms are unconvinced that even in giant cell tumor trauma is an important etiologic factor.

On rare occasions we find an osteogenic sarcoma associated with a previously incurred ossifying hematoma and in such instances it is difficult to dissociate the origin of the sarcoma from the injury which caused the ossifying hematoma, and yet the periosteal hemorrhages of scurvy are apparently never the precursor of sarcoma.

Certain cases of osteochondroma or chondromyxoma have been studied where injury has seemed to initiate a change in the type of tumor to that of chondrosarcoma, and yet only occasionally has successful extirpation of such benign tumor been followed by recurrence and a transition to fully malignant chondrosarcoma.

Therefore we believe that injury may play an important part in such transition and, as a preventive measure, removal of tumors when they occur in a location where injury is likely to occur. It must be admitted, however, that we have not yet seen such malignant degeneration in which there was no history of injury.

To summarize briefly, it would seem that the development of bone sarcoma has been the result of a combination of each case and a decision based upon known facts have not been the rule. Little has been afforded by the pathologist; it is a matter of opinion to favor it. Considering the universality of injury to be the cause of sarcoma of bone it is not surprising that they are followed by the development of sarcoma.

So-called expert testimony on matters of injury to malignant disease is not at all the opinion of an interested observer as worthy of credit. Until qualified authorities are summoned by the plaintiff or the insurance carrier, to pass upon the matter in a judicial and scientific manner, medical testimony is of doubtful value and will not enhance the value of the case.

74. THE EXPERIMENTAL PRODUCTION OF BONE SARCOMA

BIOLOGIC METHODS

IN 1929 CONNOR REPORTED HIS SUCCESS WITH THE EXPERIMENTAL PRODUCTION of Ewing's sarcoma in the tibia of Rhode Island Red chicks. Two years later Berg, working with William B. Coley, used the dried virus from the filterable fowl tumor (endothelioma) which was originally discovered in the laboratory of the Imperial Cancer Research Fund (1927) and furnished through the kindness of W. E. Gye. By using the tumors of the second and third series for inoculation, Berg was able to produce five different histologic types of tumors simulating the different types found in man. From clinical, roentgenographic, gross, and histologic examination he recognized the following types: (1) endothelioma, (2) plasma cell myeloma, (3) osteogenic sarcoma, (4) giant cell tumor, and (5) epithelial tumor (carcinoma).

RADIOACTIVE PRODUCTS

STRONTIUM

Considerable work in connection with the production of bone tumors by radioactive strontium, plutonium, and some of the radioactive rare earths has been done at the Argonne National Laboratory as a part of the Manhattan District program by Brues, Lisco, and Finkel. These investigators were particularly interested in the late or chronic effects of exposure to the fission products and to plutonium, they also studied measures to protect the personnel from dangerous amounts.

Experiments with strontium were carried out on several thousand mice. This substance, chemically similar to calcium, is mainly deposited in bone, as is radium. Its beta particles (Sr^{90}) have an energy which is chiefly dissipated within 0.5 mm. of the site of deposition. Hence bone, bone marrow, and the immediately contiguous tissues receive virtually all of the irradiation damage

As might be anticipated radioactive strontium proved to be a producer of bone tumors par excellence, even exceeding radium in this respect. About three-fourths of the tumors were osteogenic sarcomas; the remainder were fibrosarcomas.

The distribution of the tumors in the various bones closely paralleled that in spontaneous human sarcomas; 70 per cent were in the long bones of the extremities; the femur, humerus and tibia were mentioned as common sites. Metastases were found frequently, and more so in rats than in mice.

Brues and his co-workers found that the striking factor was the time interval between the injection of the radioactive strontium and the development of bone sarcoma. It appears that the time of tumor development is influenced only moderately by the dose and that after the latent period is ended "tumors appear with considerable rapidity of succession." These investigators also felt that where the bones received the radioactive agent during the period of most rapid growth they were unable to detect an acceleration of bone-tumor development, although many of the mice which had received Sr^{90} at about the time of birth did show an arrest or a stunting of growth and deformities of the atrophied long bones.

PLUTONIUM

Brues noted the development of bone sarcoma less frequently following the administration of plutonium than of Sr^{90} . This is probably due to the fact that many animals die of chronic liver damage and because the latent period of bone tumor development appears to be much longer with plutonium than with Sr^{90} .

PRODUCTION OF OSTEOGENIC SARCOMA BY CARCINOGENIC CHEMICALS

In a series of 700 tumors of mice and rats induced by subcutaneous injections of benzpyrene and of dibenzanthracene, Dunning, Curtis, and Bullock observed two osteoid sarcomas of the soft parts (containing bone and cartilage). These sarcomas were analogous to the extraskelatal osteogenic sarcoma observed in man.

Brunschwig and Bissell, by intramedullary implantation of a mixture of 10 per cent benzpyrene and cholesterol in the tibia of mice, succeeded in 1 out of 3 animals in producing an osteogenic sarcoma. This is the first recorded instance of the experimental production of an osteogenic sarcoma by a chemical agent. Brunschwig also reported the development of fibrosarcoma in the tibia in 4 of a series of 33 white rats following the intramedullary injection of methylcholanthrene; in two the tumor was parosteal and in the other two central in origin. No metastases were found in any of these animals at autopsy.

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